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Augmentation of Vasoactive Substances by Tetraethylammonium Chloride

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This investigation attempts to demonstrate the mechanism by which substances that block autonomic ganglionic transmission increase the pressor and depressor activities of a variety of drugs. Short-lived hypertension and a high degree of vascular responsiveness is induced by combining cord destruction, inactivation of the carotid sinus mechanism and nephrectomy. The increased responsiveness is found to be due to removal of the compensatory nervous mechanisms which tend to oppose changes in blood pressure. It may be reduced or abolished by hepatectomy, severe hypotension and shock.

BLOCKADE of transmission of nerve impulses within autonomic ganglia by tetraethylammonium chloride (TEAC) is now recognized as the chief action of this drug, as shown by the several penetrating investigations of Acheson, Moe, Hoobler and Lyons.[1, 2, 3, 4, 5] This blockade, as we have demonstrated,[6, 7] results in augmentation of the cardiovascular pressor and depressor responses to a variety of substances. Such increased responsiveness contrasts sharply with the refractory state of the vascular system in shock[8, 9] and may have important significance because of the probability that disease of the heart and blood vessels may result from specific changes in responsiveness to stimulation. The reasons for failure of TEAC to duplicate surgical sympathectomy is also worthy of investigation.[10]

The effects of TEAC, however, are not limited to blockade of autonomic transmission. The initial depressor response is due to blockade, but, as more and more of the drug is given, the depressor response gives way to a pressor one, caused by liberation from the liver of a noradrenaline-like substance.[11] At this stage of TEAC treatment, responses to many other drugs are greatly heightened. Since the mechanism by which increase in responsiveness occurs is not known, we have studied it, and the results are recorded in this paper.

The broad problem which is our concern is the factors which determine the responsiveness of the blood vessels in health and disease. First, it will be shown that in dogs, cat, rats and human beings, substances such as adrenalin and angiotonin are augmented in their pressor action while others such as pituitrin are not. The mechanism of augmentation is shown to be due chiefly to loss of inhibitory or compensatory nervous mechanisms elicited by the autonomic blockade. Proof of this depends on the experiments encompassing total sympathectomy, cord destruction and inactivation of the carotid sinus mechanism. A number of factors can influence the degree of augmentation, the chief of which, in our experience, are loss of the liver and terminal shock state.

Another means we have found of increasing vascular responsiveness, and hence the extent of the augmentation, is removal of both kidneys; other methods, such as injection of cocaine, methylene blue, tetramethylammonium chloride, and Dibutolin have also been tried. Decreased responsiveness has been

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sought by injection of Dibenamine, Benzodioxane and dihydroergocornine. These procedures in combinations can widely alter pressor-depressor responses.

If in such experiments as these, responses to the same dose of vasoactive drugs can be widely varied, similar variations may well occur in the course of normal physiologic adaptation. We have indeed found that, under conditions as rigidly controlled as we know, the variations in response of supposedly normal dogs to standard doses of adrenaline and l-noradrenaline ranged from zero to 110 mm. Hg.

Methods

Mongrel dogs of from 6 to 15 kilograms of body weight were given 35 mg./Kg. of pentobarbital intraperitoneally or intravenously, and the experiments started within one to one and one-half hours. A continuous slow drip of saline was given into one femoral vein and the opposite one used for injections. Arterial pressure was recorded from a femoral artery connected to a mercury manometer by polythene tubing which contained heparin solution. If the respiratory passage was not clear, a tracheal cannula was inserted. In most cases, the order in which the test drugs were given was the same. These drugs were adrenaline, U.S.P., 20 γ; l-noradrenaline (l-Arterenol*) 25 γ; barium chloride, 9 mg.; angiotonin, 5 cat units; renin, 0.1 cc.; and tetraethylammonium chloride, 5 mg./Kg.; nicotine, 0.15 cc. 1:1000 dilution; histamine, 40 γ. The details of the experimental method have previously been described.[12]

Results

Substances Showing Augmentation

Both adrenaline and l-noradrenaline are among the easiest substances to augment with TEAC. Doses of 5 mg. TEAC per Kg. body weight were given intravenously and often after the first injection some slight increase in response to pressor drugs was observed. Maximum augmentation often required 20 to 40 mg./Kg. when given in single doses of 5 mg./Kg. About the same amount was needed when given by infusion. The rate at which pressor responses increase above the control levels roughly parallels the conversion of responses to TEAC from depressor to pressor. The two rates are, however, independent of one another because slight augmentation is usually ob-

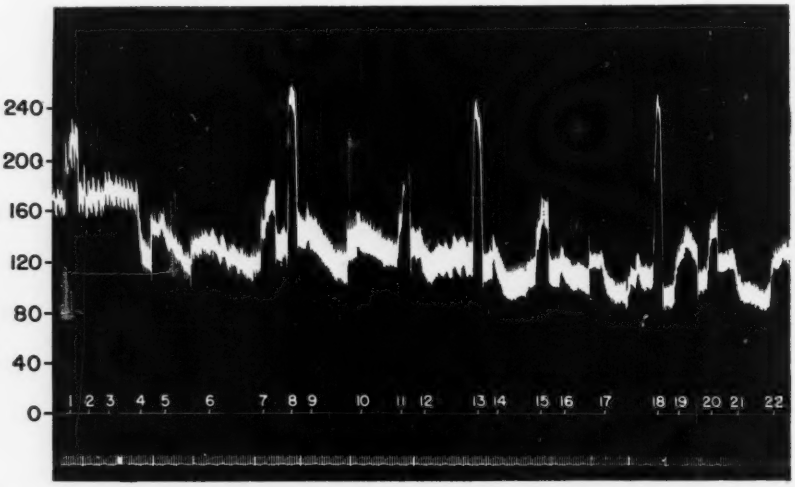

Fig. 1.—Responses of a normal dog (No. 929) under pentobarbital anesthesia showing augmentation by TEAC. (1) Noradrenaline, (2) adrenaline, (3) barium chloride, (4–6) TEAC, (7) adrenaline, (8) noradrenaline, (9–10) TEAC, (11) barium chloride, (12) TEAC, (13) noradrenaline, (14) TEAC, (15) adrenaline, (16–17) TEAC, (18) noradrenaline, (19) adrenaline, (20) barium chloride, (21) TEAC, (22) adrenaline.

* The l-Arterenol was kindly supplied by Dr. M. L. Tainter, Sterling-Winthrop Research Institute.

served before the TEAC effect becomes significantly pressor.

Barium chloride is augmented often but irregularly, and its augmentation does not parallel that of adrenaline and noradrenaline. Tyramine is easily augmented; 2-aminoheptane less easily, while the pressor effects of pituitrin, ephedrine and Paredrine are changed little if any. Depressor substances such as histamine, choline and acetylbetamethylcholine exhibit the phenomenon only moderately. Renin and angiotonin are both augmented and renin tachyphylaxis under certain circumstances is overcome. The action of renin and angiotonin will be the subject of a more detailed communication.

Thus substances of varied chemical structure exhibit the phenomenon, and some vasoactive substances, notably pituitrin, Paredrine and ephedrine, fail to show it.

Mechanism of Augmentation

Sympathectomy and Spinal Cord Destruction.—A variety of mechanisms could account for augmentation. The most likely is concerned with blockade of autonomic ganglionic transmission. This follows from the experiments illustrated in Table 1 in which it is shown that no further augmentation occurred following injection of TEAC into animals subjected to total lumbodorsal surgical sympathectomy plus inactivation of the carotid sinus mechanism. In short, if most of the autonomic ganglia regulating vasomotor responses have already been removed, TEAC has little or no augmenting action. On the other hand, in three experiments total lumbodorsal sympathectomy with supradiaphragmatic vagotomy did not prevent augmentation following TEAC. To preclude augmentation completely, both carotid sinuses and both vagus nerves had to be inactivated.

The view that augmentation is due to removal of compensatory nervous mechanisms was more thoroughly examined in a large number of dogs subjected to progressive removal of various portions of the nervous system. The operations were performed aseptically as neurosurgical procedures. Adequate recovery was allowed between stages to circumvent the profound influence of trauma and shock on vascular reactivity. The so-called "acute" experiments were largely avoided in these studies.

As we have noted elsewhere, total lumbodorsal sympathectomy does not wholly supplant TEAC augmentation although it does so to some undetermined degree. After laminectomy, the anterior nerve roots were sectioned at various levels in 22 dogs to ascertain the minimum denervation compatible with maximum augmentation of vascular responsiveness. Because there was usually some doubt at the operating table as to the precise level at which the roots were being cut, the results were reexamined at autopsy. Since this group of experiments confirm those in which the spinal cord was destroyed, details of the results will not be given. Suffice it to say that preganglionic denervation from C-6 to D-8 in most animals augmented responsiveness as much as when the operation was extended from C-6 to L-3. The augmentation was qualitatively the same after different test drugs as after actual cord destruction.

In four experiments in which dogs were decapitated between the fourth and fifth cervical vertebrae, TEAC augmented responsiveness two to three fold. Usually destruction of the spinal ganglia alone does not give full augmentation but in the absence of restraint of the remaining nervous system, their loss becomes the more important.

Destruction of the cord below the level of D-6 does not give maximum augmentation, while progressive destruction up to C-6 causes complete loss of the cord component. Thus the extremes of the area of the cord concerned with the mechanism of augmentation are included within C-6 to D-6. While cord destruction from C-6 caudad significantly augments vascular reactivity, injection of TEAC increases it still further to equal that resulting from the combined operation of inactivation of the carotid sinus mechanism and cord destruction.

Twenty-four experiments were performed in which either the cord was sectioned by the removal of a few millimeters of substance or, after section, the distal cord was destroyed by a pithing rod. We have not obtained con-

vincing evidence that section of the cord is less effective than section plus distal destruction.

sor nerves after removal of the carotid sinuses was without conspicuous effect in brief experiments. That these operations produced only

TABLE 1.—*Example of the Effect of Cord Destruction, Nephrectomy, Hepatectomy, Sympathectomy and Carotid Sinus Inactivation*

No.	Adrenaline	Barium Chloride	Renin	TEAC	TEAC	B.P.	
779	50	36	52			102	Cord destroyed C-6 ↓, (11/13/48) ne-
	54	30	30			120	phrectomy 1 day before control injec-
	56	36	30			90	tions. Carotid sinus mechanism in-
	74		30			120	activated.
	76		34	66	38	118	
	84		38	56	42	106	
	86	48	16				
774	10	6	16			66	Cord destroyed C-6 ↓ (11/1/48), Hepa-
	20	8	8			62	tectomy 11/2/48. After control injec-
	18			4	4	60	tions carotid sinus mechanism inacti-
	24	8		8		66	vated.
	20		0			84	
	30	4	8	0		80	
	14					72	Cross transfusion of 2120 cc. blood with
	18		0			76	normal dog.
763	16	30	20			136	Cord destroyed C-6 ↓ (10/18/48). After
	44	22	18			160	control injections (10/22/48) carotid
	46		0			106	sinus mechanismin activated.
	66	26	0	28		100	
	70			20	12	112	
	40	16	10			102	
756	20	14	4			108	Cord destroyed C-6 ↓ (11/11/48), hepa-
	34	10	0			100	tectomy (11/19/48). Carotid sinus
	26	16		0	10	80	mechanism destroyed after control in-
	48	18	0			102	jections.
	28	16	0	0		94	
	42	12				102	
	34	14				100	300 cc. fresh heparinized dog's blood
	24		0			102	given.
996	+12−64	24	—	10	16	104	"Total" sympathectomy
	24			12	14	104	
	44	30		30	14	86	
923	26	10	—	4	12	124	"Total" sympathectomy
	64	26		48	14	160	
314	40	76	46	12		130	"Total" sympathectomy and subdia-
	76	58	46			70	phragmatic vagotomy.

Inactivation of the Carotid Sinus Mechanism.—When only the carotid sinuses themselves were removed, vascular reactivity was unaltered. Section of vagus and/or aortic depressa partial obliteration of the compensatory nervous mechanism is shown by the fact that TEAC injections augmented responsiveness to a significant, though lesser, degree.

When the cord was destroyed from C-6 caudad a day or two before, and the carotid sinus mechanism was inactivated, no further augmentation could be induced in 26 dogs (Table 1) by injection of large amounts of TEAC. In short, this extensive surgical destruction reproduced the augmentation resulting from TEAC injections into the intact animal.

Some of our experiments suggest that carotid sinus reactivity is increased by cord destruction. Intense bradycardia and lowering of arterial pressure to between 10 and 20 mm. Hg was noted upon surgical approach to the carotid sinus in dogs whose cords had previously been destroyed. Death, although apparently unavoidable, was circumvented by severance of the vagus nerve; the blood pressure rose to normal or even hypertensive levels, and survival was assured. Vagus section saved some animals even after three-minute periods of extreme hypotension.

The Effect of the Removal of the Liver, Kidneys and Adrenal Glands On Augmentation

The Effect of Hepatectomy.—The role of the liver in the control of vascular reactivity has been dealt with in another paper.[13] We shall consider here only the alterations resulting from its removal on the augmenting effect of TEAC. Its depressor action was much increased several hours after hepatectomy, doses of 2.5 mg./Kg. producing almost fatal falls in arterial pressure in some cases. The response of these animals to adrenaline, noradrenaline, barium chloride and angiotonin was poor before TEAC and improved little, if at all, after it. Indeed, for a long time in the early experiments, we saw no augmentation in the hepatectomized animals and we were almost ready to conclude that there was none. Extension of the experiments to well over a hundred made it possible to demonstrate occasional definite augmenta-

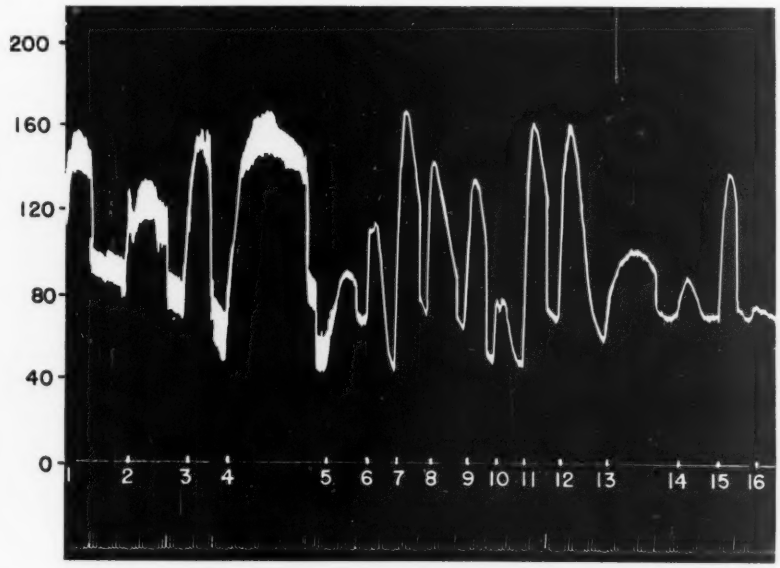

FIG. 2.—Demonstration of the moderate augmenting effect of TEA in a sympathectomized dog treated with a small dose of atropine (No. 498). The initial responses are already greater than normal. (1) Adrenaline, (2) barium chloride, (3) angiotonin, (4) renin, (5) atropine 1/100 gr., (6) TEA 5 mg./Kg., (7) adrenaline, (8) barium chloride, (9) angiotonin, (10) TEA, (11) adrenaline, (12) serotonin, (10) TEA, (11) adrenaline, (12) serotonin, (13) renin, (14) nicotine, (15) barium chloride, (16) saline 120 cc.

tion after repeated doses of TEAC. This occurred more often in animals in which nephrectomy was performed just prior to hepatectomy.

In some animals augmentation appeared so long after injection of TEAC (several hours later) that the responsibility of TEAC was questionable. The relationship between the appearance of augmentation and the dose of TEAC was difficult to determine because it was necessary to administer the drug with such care in these animals. As long as an hour might be required to introduce 10 mg./Kg., which is not ordinarily a full augmenting dose. While adrenaline and noradrenaline were, on occasion, apparently augmented by action of TEAC, renin never was and angiotonin seldom was.

When the cord had been destroyed from C-6 caudad several days before hepatectomy, injection of TEAC elicited almost no vascular response, pressor or depressor. The usual rise in arterial pressure noted in dogs after cord destruction was absent, as was the pronounced fall customary after hepatectomy alone. It was as though the two had cancelled each other out. In such animals slight, if any, augmentation to adrenaline, noradrenaline or barium chloride occurred (Table 1, experiments Nos. 774, 756). Thus, hepatectomy alone seriously reduces or abolishes the effectiveness of TEAC as an augmenting agent.

TABLE 2.—*Examples of Effect of Cord Destruction, Renal Hypertension and Nephrectomy on Vascular Reactivity*

Date	Adrenaline	Nicotine	Histamine	$BaCl_2$	Angiotonin	Renin	TEAC (100 mg.)	Ave. B.P. mm.Hg	
	42	−18+44	−42	22	17	38	+2−18	132	Average normal dogs
3/26	32	−10+8	−34	42	26	94	+16−6	102	1 hr. after cord destroyed C-6 caudad:
3/31	36	−50	−34	34	30	72	+26−58	110	still under pentobarbital, no anesthesia in following experiments
4/7	42	−74	−50	18	4	6	+64	202	Clamps on renal arteries 4/2/47
4/11	64	−42	−48	30	36	78	+14−18	138	
4/20	98	−62+38	−44	36	66	100	+26−20	144	Lt. nephrectomy 4/14/47 Rt. nephrectomy 4/19/47. No. 136
5/1	56	−28+14	−36	24	40	40	+94	110	C-7 to D-6 inclusive removed 4/29/47
5/9	74					102		84	
5/13	100	−12+28		62	106	102	+88	106	Bilateral nephrectomy 5/12/47. No. 169
4/16	86	−54+22	−40	36	32	68	+36−30	140	8 hrs. after cord destroyed C-6 caudad
4/19	96	−72+56	−48	36	32	154	+36−20	140	Bilateral nephrectomy 4/17/47. No. 161
10/6	50			22		36		130	Cord destroyed C-6 10/4/48
10/8	50			18		98		128	Nephrectomy 10/6
10/8	44			22		50	30	172	Inactivation carotid sinus mechanism
	74			40		68	36	176	
	80			32		46	26	174	
	86			24		44	30	174	
	92			28		60	32	150	

Nephrectomy and Adrenalectomy. —TEAC caused augmentation with or without anesthesia in dogs nephrectomized one to three days before. Nephrectomy alone increased the responses especially to renin and angiotonin and, with the addition of TEAC, the animals exhibited a heightened degree of sensitivity to adrenaline, noradrenaline and barium chloride as well.

We have observed that the initial responses to TEAC in nephrectomized dogs were pressor, as though they had already received TEAC. This suggests that nephrectomy may cause the retention of substances able to institute

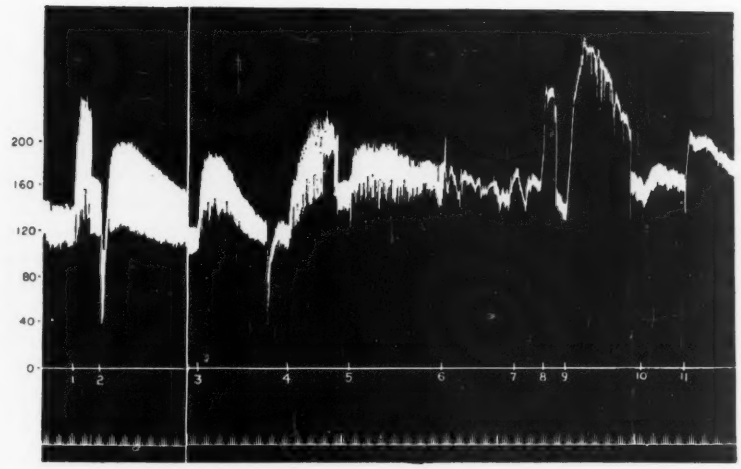

FIG. 3.—Demonstration of the increase in responsiveness elicited by TEAC in a dog already showing augmented response due to cord destruction from C-6 caudad and nephrectomy (No. 163). (1) Adrenaline, (2) nicotine, (3) angiotonin, (4) renin, (5) barium chloride, (6–7) TEAC, (8) angiotonin, (9) renin, (10) nicotine, (11) barium chloride.

TABLE 3.—*Example of Effects of Nephrectomy and Cord Destruction*

No.	Adrenaline	Noradrenaline	Barium Chloride	Renin	TEAC	TEAC	TEAC	B.P.	Days After Operation
872	8	44	18		−40	−50	0	126	1 day after nephrectomy
				18	0	20		156	
872	24	100	50		0	46	64	184	2 days
	12		38	38				204	
872	26	50	20	24	12	0	20	160	3 days
	20		22		24			156	
882	16	80	14		−50	−24	−14	162	1 day after nephrectomy
					24			142	
	64		58		50			160	
883	42	102	20		−22			124	2 days + adrenalectomy
	50		16		0	0	0	116	
	62				0	0	8	134	
	42	40							
952	52	108	32	48	66	32	32	184	cord destruction C-6 ↓
		202			34	42	60	190	nephrectomy 1 day; vagotomy
					56	36		204	
	100	156	24		36	26	46	180	
937	60	100	8	108	26	12	12	188	cord destruction C-6 ↓
	58		6		8	8	8	182	nephrectomy 1 day before
	68	90			24	16			
	52			48					

autonomic ganglionic blockade. However, the mechanism may be entirely different.

When bilateral adrenalectomy was performed almost an hour before the experiment and the animals allowed either to recover from ether anesthesia or to continue anesthetized with

pentobarbital, no significant change in vascular reactivity was detected. The long term effects of adrenalectomy in relationship to salt and steroid administration will be considered in another communication. We were also unable to detect an adrenal participation in the responsiveness of nephrectomized dogs and in 3 animals in which the cord had been destroyed and the kidneys removed.

The carotid sinuses of dogs subjected to nephrectomy and cord destruction from C-6 caudad were highly sensitive. Cardiac arrest occurred when the sinus was approached surgically unless the vagus nerves had been previously cut. The same phenomenon occurred in three of the dogs with the adrenal glands removed as well.

Augmentation occurred with TEAC after nephrectomy, adrenalectomy or both and even occurred when the cord was destroyed from C-6 caudad unless the carotid sinus mechanism was inactivated.

Hypertension in dogs with the cord destroyed, carotid sinus mechanism inactivated and the kidneys removed is an interesting phenomenon which we have noticed repeatedly. Examples are dogs No. 942 and 937 in Table 3. Injection of TEAC into such animals gave sharp rises in arterial pressure and the rise following injection of renin persisted sometimes for hours. Hypertension was not attributable to pentobarbital anesthesia, which was not used in these animals because their cords were cut. In most of these animals, TEAC produced little augmentation; further, it did not lower the average arterial pressure, as would be expected if the hypertension were due to autonomic hyperactivity.

Influence of Periods of Severe Hypotension and Shock on Augmentation and Vascular Response.

In normal, hepatectomized or nephrectomized-hepatectomized dogs, periods of severe hypotension (20 to 50 mm. Hg) even of short duration may elicit a period of refractoriness which is little, if at all, relieved by TEAC. An attempt has been made in a number of these hypotensive animals to overcome the refractoriness by elevating and maintaining the pressure at normal levels by intra-arterial transfusion of saline-blood mixtures. Temporarily, the response may be heightened, and after TEAC such easily augmented substances as noradrenaline show some increase in pressor response, but it is seldom maintained, particularly in the hepatectomized animals where the vessels respond similarly to those of animals in terminal shock. Until responsiveness returns, the life of the animal is in danger.

It should, however, be made clear that repeated observation shows no necessary relationship between arterial blood pressure and vascular responsiveness. Rather, responsiveness appears to be related to the length of time hypotension has existed, as well as to the acuteness of its occurrence. We have come to doubt seriously that, within limits, a ceiling exists which prevents even at already elevated pressures further rise on injection of stimulating substances on a floor from which greatly increased responses may be expected. Some highly responsive animals have been those with experimental renal hypertension in which the initial pressure was over 200 mm. Hg and some of the poorest responses have occurred in animals with initial arterial pressure of from 70 to 90 mm. Hg.

The results of our study of the prophylactic and therapeutic effects of TEAC injection in shock have been published.[9] Suffice it here to add further experience we have had in the last three years. It has not been possible without trial to forecast the occurrence of augmentation in an animal with severe hypotension or shock. Sometimes augmentation is remarkable; more often it fails completely. If TEAC elicits augmentation when shock has occurred, both noradrenaline and adrenaline are much easier to augment than renin. While an augmented response to adrenaline is compatible with a low arterial pressure, the chances of its rising are much improved with return of responsiveness and augmentation with TEAC.

Other Means of Altering Vascular Responsiveness.

Procaine and Cocaine Injections.—Five cc. of 2 per cent procaine was injected intravenously into unanesthetized dogs after the

control test drug injections had been made. The response to nicotine temporarily disappeared but no appreciable augmentation was noted with the other drugs. Then TEAC was injected and augmentation occurred. When large amounts of cocaine (2 doses of 10 mg./Kg. intravenously plus 10 mg./Kg. intramuscularly) were given the adrenaline response was greatly augmented. Barium chloride was slightly augmented but angiotonin and renin were not. If TEAC was then given, little further augmentation occurred. Both angiotonin and barium chloride were slightly augmented. Cocaine given after large doses of TEAC often further increases adrenaline response, but the augmentation is sharply limited by the toxic effects of cocaine. The renin response may be somewhat aided if tachyphylaxis is not induced but does not reach the high levels which usually follow repeated injections of TEAC alone. If tachyphylaxis is elicited, then cocaine alone or followed by TEAC does not overcome it.

Methylene Blue.—In 6 experiments, 0.2 grams of methylene blue gave moderate augmentation of the adrenaline response in most cases but none to renin.

Dibutolin.—Repeated injection of 20 mg. doses Dibutolin,[5] in experiments performed several years ago, showed it to cause moderate augmentation especially to adrenaline, confirming the recently published work of Moe. After about 100 mg. of Dibutolin had been given, TEAC caused little further augmentation of adrenaline or barium chloride.

Dibenamine.—Doses of 20 mg./Kg. were given intravenously to 10 nephrectomized dogs. As soon as the response to adrenaline was clearly depressor, TEAC was given in repeated doses. No augmentation of the adrenaline response occurred.

*Dihydroergocornine.**—Repeated injection of 0.5 mg. doses had no effect on the response to angiotonin and barium chloride but in some dogs the adrenaline response was reversed. Administration of TEAC now caused no augmentation. The pressor action of noradrenaline seemed a little affected by doses of 2 mg. of dihydroergocornine, which were enough to cause sharp reversal of adrenaline. In other dogs, the response was reduced but not reversed. We were constantly impressed by the variety of response elicited in different dogs by this drug, both as to its pressor action and blocking effect on adrenaline.

Tetramethylammonium chloride.†—This drug, so closely related to TEAC, in repeated doses of 1 mg./Kg. caused nothing but repeated rises of arterial pressure and no augmentation.

Augmentation in Patients.

Augmentation of the adrenaline and angiotonin responses has been observed in 3 patients after injection of large doses of TEAC, just as in animals. One of these patients had suffered a massive intracerebral hemorrhage, another a cerebral thrombosis, and the third had had resection of 1 cm. of the cord at D-1 for intractable pain resulting from removal of multiple meningiomas from the spinal canal. The results from the latter are shown in Table 4. There is no doubt that the phenomenon is not limited to dogs, cats and rats with or without anesthesia.

TABLE 4.—*TEAC Augmentation in a Patient with Cord Severed at D-1.*

10-16-47. Cord ligated and severed at D-1. Horner's syndrome was transiently present. Perspired over left leg. Cannulated dorsalis pedis.

Time		B.P. Change	Average B.P.
2:27	0.1 cc. 1/10,000 adrenaline	+30	90
2:30	0.5 cc. 1/1000 nicotine	−18	92
2:35	2.5 cc. barium chloride 18 mg./cc.	+36	90
2:53	2.0 cc. angiotonin 10 u./cc.	+66	110
3:01 to 3:08	500 mg. TEAC	−50	120
3:11	0.1 cc. 1/10,000 adrenaline	+56	64
3:21	0.1 cc. 1/10,000 adrenaline	+52	70
3:27	2.5 cc. barium chloride	+42	86
3:33	100 mg. TEAC	−28	118
3:38	1.0 cc. angiotonin	+74	86

* We wish to thank Dr. Kenneth Ericson, of Sandoz Chemical Company, for the dihydrogenated ergot alkaloids.

† We are indebted to Dr. E. C. Vonder Heide of Parke-Davis and Company for this drug.

Discussion

In examining the data which we present, the following average responses in mm. Hg furnish the control values: adrenaline, +45; nicotine, +44; histamine, −42; barium chloride, +22; renin, +38; angiotonin, +17; TEAC, + 10–38 mm. Hg. Since there is wide variation from dog to dog, large numbers of experiments are necessary to assure their significance. We have included in the protocols only examples of the experiments, not so many as to burden the reader unduly and yet, we hope, sufficient to indicate the character of the changes. In most cases, they are great enough to leave no doubt of their validity in the observer's mind.

As the work progressed, it became apparent that so-called "acute" experiments in which the nervous system was roughly handled often lead to contradictory results. For example, pithing in many cases yielded uninterpretable results. In some pithed animals, TEAC seemed to cause augmentation, while in others it did not. Consistency greatly improved when the experiments were conducted as neurosurgical operations and suitable periods of recovery allowed.

A variety of substances show augmentation, but what determines which ones is not clear. We have used test drugs with primary cardiac action as well as those acting more peripherally. Augmentation is not characteristic of one or the other.

We share with Moe the hypothesis that the simplest mechanism accounting for augmentation would be blockade of the compensatory nervous mechanisms which control the homeostasis of the arterial pressure. The proof that this is so is found in the demonstration that after cord destruction from C-6 caudad, plus inactivation of the carotid sinus mechanism, TEAC gives no further augmentation. This was not so easy to prove as might have been expected, because of spontaneous alterations in sensitivity over the period of hours while TEAC was being injected. Whatever the explanation, some dogs, after every reasonable care had been taken to insure adequate surgical denervation, still showed moderate further augmentation, especially when TEAC was repeatedly injected in the course of several hours.

From our experiments the area of cord most concerned with augmentation is from C-6 to D-6, as shown by preganglionic denervation and by cord section. Destruction of the cord distal to the point of section did not affect augmentation significantly. Nor did destruction of the carotid sinuses and aortic depressor nerve mechanisms or decapitation alone greatly reduce the augmentation which TEAC induced. However, in animals with cord destruction plus ablation of the carotid sinus mechanism, with the exception of a few animals in which over a period of several hours some augmentation occurred, TEAC caused no further augmentation. Thus destruction of a part of the nervous mechanism controlling augmentation without removal of the whole of it often leads merely to the taking over by the remainder of the neurogenic control of vascular reactivity. As a corollary, an increase in sensitivity of the residual mechanism often becomes demonstrable.

Further support of this concept was furnished by the behavior of the carotid sinus mechanism when the cord was destroyed from C-6 caudad. It became more active than normal, for, unless the vagus nerves were severed before the carotid sinuses were manipulated during operation, fatal bradycardia and hypotension occurred. Resuscitation often occurred as long as two to three minutes after apparent death when the nerves were severed following sinus irritation. It appeared as though the slowing of the heart was so intense as to cause the death of the animal.

Fitting with the view that an incomplete denervation often influences augmentation little, if at all, is the demonstration that inactivation of the carotid sinus mechanism alone has an insignificant effect. Adding cord destruction to C-6 completes the denervation and elicits maximum augmentation not further enhanced by large doses of TEAC.

The evidence is insufficient to determine the precise mechanism of the action of liver extirpation on TEA augmentation. When hepatectomy alone is performed the animals exhibit increased sensitivity to the depressor

action of TEAC, presumably because one of the compensatory mechanisms—the secretion by the liver of a noradrenaline-like substance—has been removed.[11] Augmentation in most cases is extremely poor, if it is observed at all. It is somewhat more likely to occur when nephrectomy has just preceded hepatectomy, the presumption being that the removal of the kidneys removes the source of renin which may be secreted during the operation of hepatectomy, making the animal tachyphylactic to its own renin. Further, since nephrectomy itself increases responsiveness, the chances for augmentation to occur are improved. Thus, the fact that TEAC exhibits little augmentating effect after hepatectomy could be due to the facts (*1*) that the response of the blood vessels is depressed and is not increased by denervation induced by TEAC and (*2*) that the autonomic nervous system, as a result of hepatectomy, has so lost its controlling force on vascular reactivity that its blockade by TEAC no longer results in augmentation.

Nephrectomy, as we have noted, increases response to various substances, but TEAC is still able to augment further their activity. Since the initial doses of TEAC were often pressor in such animals, it suggests the possibility that nephrectomy causes the retention of autonomic blocking substances.

The permanent loss of all of the neurogenic compensatory mechanisms of which we are currently aware, along with the sensitizing effect of nephrectomy, leaves the animal highly vulnerable to pressor stimuli. It is not surprising, therefore, that in animals in good clinical condition chronic hypertension of the order of 160 to 180 mm. Hg may be observed. Injection of renin further increases it, the effects sometimes lasting for hours. That such a mechanism might be in part responsible for the hypertension of simple nephrectomy is evident. Except in severe adrenal insufficiency, we have not observed significant deviations from the normal responsiveness to any of the test drugs in adrenalectomized dogs. Augmentation accompanies regularly the injection of large amounts of TEAC.

An attempt has been made with only slight success further to increase responsiveness by injection of cocaine. When the full response is obtained after large doses of TEAC, cocaine injection further increases the adrenaline response, possibly by protecting it from inactivation. The amount of cocaine required to produce the result is sufficiently large to limit the usefulness of animals so prepared.

The augmenting action of TEAC may also be reduced or blocked by a variety of substances acting on different parts of the neurovascular systems. Thus dihydroergocornine and Dibenamine in some dogs block augmentation of adrenaline or noradrenaline by TEAC. If the predominant sites of blockade by dihydroergocornine and Dibenamine are, respectively, central and peripheral, either site suffices to block the augmenting action of TEAC. It is surprising that so closely related a substance as tetramethylammonium chloride in repeated doses of 1 mg./Kg. produced no augmentation. Its effect was purely pressor, even on the initial dose.

It should be noted that periods of severe hypotension as well as shock elicit a hyporeactive state of the vascular tree[7, 8] which is not usually overcome by administration of TEAC. Occasionally, however, augmentation is dramatic, responsiveness quickly returns, and arterial pressure usually rises.

We have not tried to elicit maximum augmentation in patients because of the very large and variable doses of TEAC required (at least 1800 mg. if figures derived from dogs are valid). In two moribund patients with cerebral injury and one conscious patient with the cord severed at D-1, we have, however, given large doses with striking augmentation. It is likely that the reason Moe[2] found little augmentation was that insufficient amounts of the drug were given.

There has now accumulated enough clinical experience to validate our warning of several years ago that an unfavorable turn in patients who have had large doses of TEAC should be treated with adrenaline with more than usual caution.[6] During an emergency, adrenaline is of necessity given by vein and not subcutaneously or by carefully controlled infusion as in the pharmacology laboratory where the outcome is not critical. In one normal young girl,

for instance, during the drug test, arterial pressure became imperceptible. Injection of the usual amounts of adrenaline by vein led to pressure of well over 300 mm. Hg and gross cardiac irregularity. For the first half hour it seemed more likely that she would perish from the adrenaline hyper- rather than the TEAC hypotension.

Summary

1. Vasoactive substances such as adrenaline, noradrenaline, angiotonin, histamine and barium chloride exhibit augmented activity after intravenous injection of large doses of tetraethylammonium chloride into dogs, cats, rats and man. Other substances such as pituitrin and Paredrine fail to do so.

2. Cord destruction from C-6 caudad, "total lumbodorsal sympathectomy" and sympathectomy with supradiaphragmatic vagotomy in chronic experiments elicit increase in responsiveness but augmentation with TEAC still occurs.

3. Sympathectomy or cord destruction combined with inactivation of the carotid sinus mechanism successfully reproduces the augmenting effect of TEAC and may be used to supplant it. TEAC does not cause augmentation after these combined operations.

4. The limits of spinal nerve distribution involved in augmentation were determined by preganglionic denervation ("anterior nerve root section") and spinal cord destruction from C-6 to D-8.

5. Two examples are given of local increase in nervous sensitivity as a result of removal of interdependent portions of the nervous system. First, when the cord is destroyed from C-6 caudad, the carotid sinus may become highly sensitive. Second, when a dog is decapitated, the spinal ganglia which in the intact animal show little activity, become sufficiently active that TEAC gives conspicuous augmentation when these ganglia are blocked by it.

6. Hepatectomy reduces or abolishes the augmenting action of TEAC. While augmentation to adrenaline and noradrenaline may occasionally occur in small degree, none has been observed with renin.

7. Nephrectomy after one to two days increases vascular responsiveness which may be augmented by TEAC. Combined cord destruction from C-6 caudad, carotid sinus inactivation and nephrectomy causes greatly heightened vascular responsiveness not further enhanced by TEAC.

8. Adrenalectomy in acute experiments does not alter the power of TEAC to cause augmentation. There is also no change in this respect in animals with cord destruction and/or nephrectomy.

9. Hypertension persisting for many hours may occur in conscious dogs with cords destroyed from C-6 caudad, carotid sinus mechanism inactivated and the kidneys removed. Renin injection causes a further increase in arterial pressure which may persist for hours.

10. Severe hypotension and/or shock induces refractoriness of vascular response which is not usually overcome by TEAC. There is, however, no definite relationship between the height of the blood pressure and vascular responsiveness. Sometimes after periods of severe hypotension, augmentation by TEAC is great.

Conclusions

The greatly increased response to many vasoactive drugs elicited by tetraethylammonium chloride (TEAC) in large doses is due to blockade of sympathetic ganglia and the carotid sinus mechanism, so removing their regulatory function. This augmented responsiveness may be reduced or abolished by hepatectomy, periods of severe hypotension and shock. On the other hand, while nephrectomy of itself increases vascular responsiveness, it may be further increased by TEAC.

An exceptionally high degree of vascular responsiveness is induced by the combined operations of cord destruction from C-6 caudad, inactivation of the carotid sinus mechanism surgically or by TEAC, and nephrectomy. Arterial hypertension of necessarily limited duration nay follow such operations. Removal of one part of interdependent blood pressure regulatory mechanisms of the nervous system often increases the sensitivity of the remaining complementary parts.

ACKNOWLEDGMENT

We wish to express our gratitude to Dr. Ralph Prince, Dr. Charles Devine, Mr. William West, Mr. Ralph Edmonds and Mr. Robert Parker for their help in some of these experiments.

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Ebstein's Anomaly of the Tricuspid Valve

Report of Three Cases and Analysis of Clinical Syndrome

By Mary Allen Engle, M.D., Torrence P. B. Payne, M.D., Caroline Bruins, M.D., and Helen B. Taussig, M.D.

In Ebstein's anomaly the tricuspid valve is displaced downward so that the upper portion of the right ventricle is incorporated in the right auricle. This impairs the efficiency of the right side of the heart and produces a distinctive syndrome, which is described here for the first time. Diagnosis is important because this malformation, which is not amenable to surgery, may be confused with the tetralogy of Fallot.

EBSTEIN in 1866[1] first described a congenital malformation of the tricuspid valve in which the leaflets are fused into a membranous structure, which extends like a basket down into the cavity of the right ventricle and separates the ventricle into a proximal and a distal chamber. The proximal portion is continuous with the right auricle, and the distal portion, which functions as the right ventricle, includes the outflow tract of the right ventricle.

Often the valve leaflets are completely fused with the ventricular endocardium over large areas so that it is difficult to identify the individual cusps with certainty. The anterior leaf is usually the largest, the posterior leaf usually the most malformed. Sometimes the origin of the valve leaflets posteriorly appears displaced downward from the normal site at the annulus fibrosus toward the apex of the right ventricle. Medial to the anterior leaflet there is an opening into the functional portion of the right ventricle. The right ventricle above the valve is exceedingly thin-walled. The foramen ovale in most of the cases is anatomically and functionally patent.

Since Ebstein's original case there have been 22 such malformations reported.[2–19] Including the 3 patients herein described, the total number of recorded instances of this malformation is 26.

In all of the reports in the literature the diagnosis of Ebstein's anomaly has been made only at postmortem examination. Yater and Shapiro[12] in their review in 1937 stated that "it would appear impossible to make the diagnosis during life." We have recently studied three patients with Ebstein's malformation of the heart and have re-examined the case previously reported by Taussig.[19] Although the correct diagnosis was not made during life, an analysis of these cases has revealed several features of this malformation which are sufficiently characteristic to permit clinical diagnosis.

The diagnosis is of more than academic interest, because when there is cyanosis and a diminished pulmonary blood flow, this malformation may resemble the tetralogy of Fallot. Indeed, in two of our cases (Cases 2 and 3) operation to increase the blood supply to the lungs was undertaken. Both patients died following the operative procedure.

From the Cardiac Clinic of the Harriet Lane Home of the Johns Hopkins Hospital and the Departments of Pediatrics and Pathology of Johns Hopkins University.

Case Reports

Case 1.—G. C. (HLH No. A 61737), a 10 year old white girl, was examined in the Cardiac Clinic in March, 1948.

Past History and Present Illness: A heart murmur was noted at birth, and the family was informed that she had congenital heart disease. Nothing is known concerning her color at birth, but she was kept in oxygen for the first three days. Throughout early childhood she had infrequent attacks of "violent pains" in her abdomen and seemed tired for the rest of the day. During the attacks her color was "peculiar." In retrospect the mother thought that the patient had been cyanotic during these episodes. The child was never robust, but she played with the other children and started school at the normal time.

When she was 7 years old, she was taken to the family physician for a routine examination. He found that her heart was enlarged (cardiothoracic ratio of 68 per cent) and, although she was asymptomatic, thought that she had acute rheumatic fever. She was put to bed and given salicylates for three weeks; after three months she was allowed to get up.

At the age of 8 years cyanosis occurred after exertion, and she felt tired and weak. She was examined by one of us (H. B. T.), who found a greatly enlarged heart with a rough systolic and diastolic murmur which simulated a pericardial friction rub. Teleoroentgenogram of the chest showed an increase in the cardiothoracic ratio to 75 per cent. The diagnosis was made of pericarditis superimposed on a congenital malformation of the heart. A period of bed rest with salicylates and sodium bicarbonate medication was advised.

Thereafter the patient's cyanosis increased progressively, and by the age of 9 years cyanosis was constantly present. Dyspnea was never a striking feature. She could walk four blocks very slowly before becoming tired, but she did not squat to rest. She seemed exhausted much of the time. She was given digitalis for a month without improvement; therefore, digitalis was discontinued. Four weeks before her visit to the clinic, she had a brief "fainting spell" during which she became unconscious, intensely cyanotic, and had an involuntary bowel movement. She experienced a similar episode on admission to the Harriet Lane Home.

Physical Examination: Temperature 37 C.; pulse 104 per minute; respirations 26 per minute; blood pressure 110/86 mm. of Hg. She was a tall, thin, 10 year old girl who had slight cyanosis of the mucous membranes and nailbeds at rest. The cyanosis was of equal distribution over the body. There was no clubbing of the fingers or toes. The left chest anteriorly was more prominent than the right. There was no Broadbent's sign. Her heart was greatly enlarged to the right and to the left. The point of maximal impulse was in the anterior axillary line in the fifth left interspace. No thrill was palpable. The heart sounds were almost inaudible; there was a gallop rhythm. There was a rough, soft, to and fro systolic and diastolic murmur heard all over the precordium and over the lung fields anteriorly. The murmur sounded scratchy in the fourth interspace over the sternum. Over the left chest posteriorly and maximal at the left base, there was a very loud, rasping, systolic murmur; this murmur was less well heard over the right chest posteriorly. The liver was palpable 1 cm. below the right costal margin. It was firm but was neither tender nor pulsatile. The pulses in the extremities were equal and of small volume. There was no venous distention nor peripheral edema.

Laboratory Findings: Fluoroscopy revealed a tremendously enlarged heart. It almost filled the left chest and extended far into the right chest. The base of the cardiac shadow appeared narrow in comparison with the bulk of the body of the heart. The cardiac pulsations were of exceedingly small amplitude. Because of these findings the possibility of a pericarditis and a pericardial effusion were considered, but nothing was found to substantiate the diagnosis. In the right and left anterior-oblique positions, the right ventricle extended to the left anterior chest wall and was flattened against it for a distance of several centimeters. This was interpreted as indicating a huge right ventricle. In the left anterior-oblique position, the heart posteriorly completely overlapped the spine even at 80 degrees of rotation. For this reason the left ventricle was considered enlarged. There was no prominence of

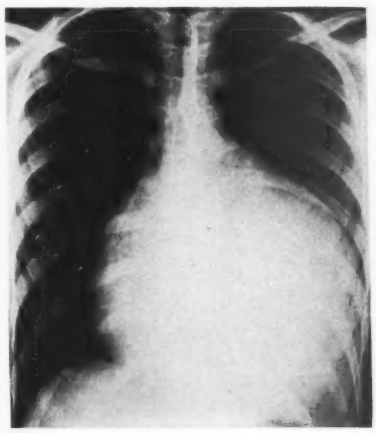

FIG. 1.—Anterior-posterior view of chest. Case 1. Note great cardiac enlargement, absence of fullness in the region of the pulmonary conus, and diminished vascularity of the lung fields.

the pulmonic conus region. The pulmonary arteries were obscured by the heart anteriorly but with rotation were seen to be of normal size without pulsations. The lung fields were unusually clear. Barium swallow showed evidence of a left aortic arch but no left auricular enlargement. The teleoroentgenogram (figs. 1 and 2) showed the cardiothoracic ratio to be 77 per cent.

The standard limb leads and the unipolar precordial leads of the electrocardiogram showed prolonged A-V conduction time and right bundle branch block. The P waves were high and peaked. The hemoglobin level was 19.8 Gm. (137 per cent). The red blood cell count was 7.2 million per cu. mm.; the hematocrit reading was 61. The white blood cell count and the differential count were normal. The sedimentation rate was 2 mm. in one hour uncorrected. Studies of the arterial blood revealed an oxygen content of 19.7 volumes per cent with a

capacity of 26.4 volumes per cent, giving an arterial oxygen saturation of 74 per cent. The carbon dioxide content was 39.4 volumes per cent. The arm-to-tongue circulation time determined with Decholin was prolonged to 20 seconds. (In our experience the upper limits of normal for a circulation time so determined is 12 seconds for a patient of this size.) Tuberculin tests were negative up to 1.0 mg. of old tuberculin.

Clinical Impression: This patient presented a diagnostic and therapeutic problem. Because of the large heart, the poor heart sounds, the scratchy to and fro murmur which simulated a friction rub,

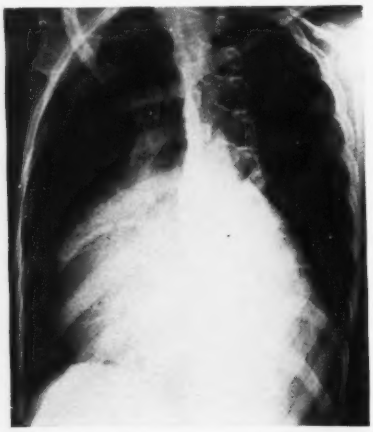

FIG. 2.—Left anterior-oblique position, taken at angle of rotation of 60 degrees. Case 1. Note enlargement of the right ventricle, which is flattened anteriorly against the left anterior chest wall, and the extent to which the enlarged right ventricle has displaced the left ventricle posteriorly.

the gallop rhythm, and the decreased amplitude of pulsations under the fluoroscope, it was postulated that she had chronic pericarditis, most likely rheumatic in origin, superimposed on a congenital heart defect. The nature of the congenital malformation was puzzling.

Course: After a ten day stay in the hospital, she was transferred to a convalescent home for a period of bed rest. There her heart continued to enlarge. On the morning of her twentieth day in the convalescent home, while lying in bed, she suddenly died.

Postmortem Examination: Autopsy No. 21188, performed by Dr. Payne. On opening the thoracic cavity, the heart was seen to occupy over three-fourths of the transverse diameter of the chest. Its great size was due entirely to the tremendous dilatation of the right auricle and the right ventricle. The left ventricle, which was essentially normal in size, was completely concealed behind the huge right ventricle.

The heart weighed 260 grams (normal approximately 150 grams). The pericardium was normal, and there was no fluid in the pericardial cavity. The superior and inferior venae cavae entered the right auricle, and the pulmonary veins entered the left auricle in the normal fashion. The orifice of the coronary sinus was wide. The right auricle was hypertrophied as well as dilated. The foramen ovale was patent, measuring 1.5 cm. in greatest diameter. Although it contained a valve, in the dilated state of the right auricle this valve was incompetent.

The tricuspid valve was grossly malformed (fig. 3). It was ballooned downward into the right ventricle and in places fused with the ventricular endocardium and in other places closely bound to it by short chordae tendineae and small papillary muscles. In the region of the infundibulum of the right ventricle, it formed a redundant membrane which divided the right ventricle into two parts: a small, distal outflow chamber which emptied into the pulmonary artery, and a much larger proximal chamber continuous with the right auricle through the unprotected tricuspid valve ring. This ring measured 12 cm. in circumference.

The leaflets of the tricuspid valve were so malformed that they could not be individually identified. On the septal portion of the auriculoventricular ring, there was no free valve leaflet distinguishable from the smooth endocardial surface. About 1 cm. distal to the ring, however, there was on the septal endocardium a small, irregular, raised area which measured 1 cm. in diameter and probably represented a malformed portion of the tricuspid valve. From the remainder of the auriculoventricular ring, there arose a large leaflet which extended into the ventricular cavity closely bound to its wall. This leaflet blended distally with the septal endocardium except in the region of the infundibulum of the right ventricle, where it presented a free margin for a distance of 5 cm. There were two fenestrations in this leaflet; one measured 1 cm. and the other 1.5 cm. in diameter. Both of these openings were held close to the ventricular wall by short chordae tendineae and papillary muscles so that they were functionless. The main communication between the two chambers of the right ventricle was through an opening formed by the redundant free margin of the valve and the prominent moderator band. This opening would have closed during ventricular systole; therefore, the valve was competent. The moderator band was enlarged; it measured 3 cm. in length and 1 cm. in diameter. It stretched across the ventricular cavity from the right ventricular wall to the septum.

The wall of the right ventricle proximal to the tricuspid valve was very thin (fig. 4); in some places it measured not more than 2 mm. in thickness. Microscopically the muscle fibers were normal in appearance but were reduced in number. Irregular

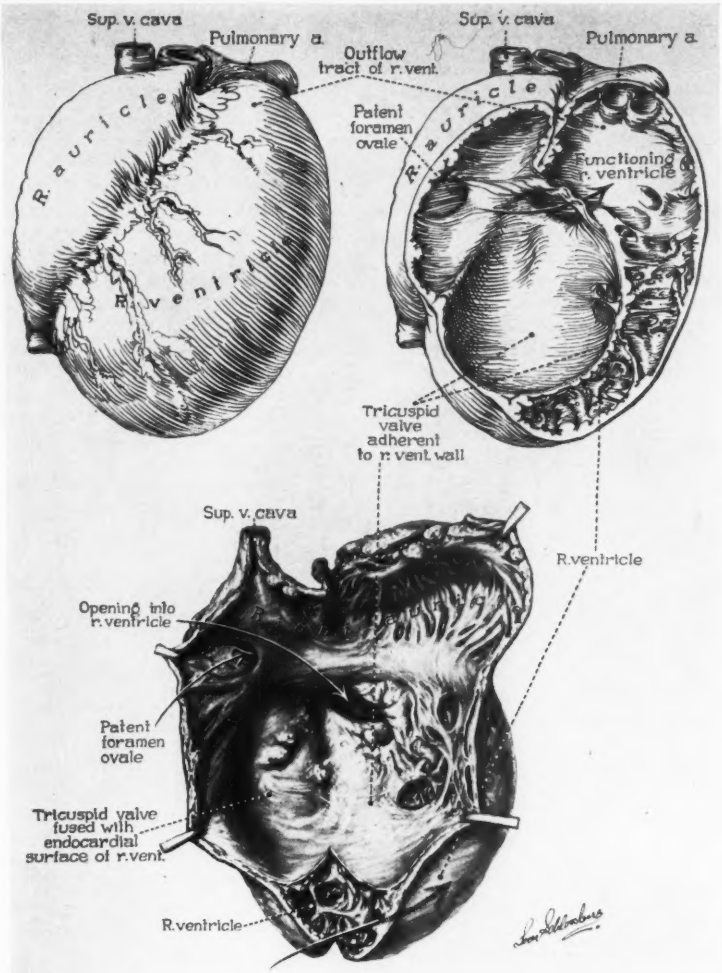

FIG. 3.—Ebstein's anomaly of the heart. Case 1. Upper drawings show the great enlargement of the right auricle and the right ventricle, the patent foramen ovale, and the anomalous position of the tricuspid valve. Lower drawing shows the interior of the right auricle and the manner in which the tricuspid valve is fused with the endocardium of the thin-walled right ventricle. The opening from the large proximal chamber into the functional portion of the right ventricle is illustrated.

FIG. 4.—Section through tricuspid valve ring. Case 1. *A* indicates right auricular wall, *V* the right ventricular wall, and *T V* the tricuspid valve leaflet. The thinness of the right ventricular wall as compared with the right auricular wall is apparent. The portion of the valve leaflet shown in this section is not fused with the ventricular endocardium.

muscle trabeculae arose from the right ventricle in the region where the valve leaflet blended with the septal endocardium. Below the displaced valve the myocardium of the right ventricle was 5 mm. in thickness and microscopically was normal.

The pulmonary valve was normal; the valve ring measured 4.5 cm. in circumference. The pulmonary artery was normal in size. The ductus arteriosus was closed. The ventricular septum was intact. The left auricle, the mitral and aortic valves, and the aorta were normal. The left ventricle was slightly hypertrophied; its wall measured 9 mm. in thickness. The coronary arteries were grossly normal, but microscopically moderate sclerosis was seen. There was moderate chronic passive congestion of the liver and pancreas.

Anatomic Diagnosis: Congenital malformation of the heart. Ebstein's anomaly of tricuspid valve. Patent foramen ovale. Congenital hypoplasia of right ventricular myocardium. Hypertrophy and dilatation of right auricle. Extreme dilatation of right ventricle. Prominent moderator band. Moderate sclerosis of coronary arteries. Chronic passive congestion of liver and pancreas.

Case 2.—J. T. H. (HLH No. A 44703), a 5 year old white boy, was first examined in the Cardiac Clinic at the age of 3 years in December, 1945.

Past History and Present Illness: At the age of 2 days a heart murmur was heard, and he was diagnosed as a "blue baby." Dyspnea was never as apparent as the cyanosis. He tired easily and rested often, but he never squatted to rest. At the time of his first visit, he could walk only one hundred feet before becoming tired.

Physical Examination: Temperature 37 C.; pulse 112 per minute; respirations 30 per minute. The blood pressure could not be obtained by auscultation, but by palpation the systolic pressure was 90 mm. of Hg. He was a moderately well developed and well nourished boy who was quite cyanotic when crying. His fingers and toes were clubbed. There was a precordial bulge. The heart was enlarged to percussion. The heart sounds were so distant that they were heard only with difficulty. There was a gallop rhythm. There was a soft, blowing, systolic murmur over the entire precordium. The liver was palpable 2½ fingers breadth below the right costal margin; it was not pulsating. There was no peripheral edema.

Laboratory Findings: Fluoroscopy showed the heart to be enlarged to the right and to the left. There was enlargement of the right auricle and the right ventricle. In the left anterior-oblique position the left ventricle overlapped the spine at 60 degrees of rotation. There was no fullness in the region of the pulmonary conus. The lung fields were remarkably clear. A barium swallow demonstrated a left aortic arch and no evidence of left auricular enlargement. The teleoroentgenogram showed the cardiothoracic ratio to be 63 per cent (fig. 5). The electrocardiogram showed first degree heart block and right bundle branch block. The P waves were high and peaked. The hemoglobin level was 27.5 Gm., and the red blood cell count was 8.55 million per cu. mm. An arterial blood sample obtained when the patient was crying revealed an oxygen content of 8.7 volumes per cent, an oxygen capacity of 28.2 volumes per cent, and an arterial oxygen saturation of 31 per cent. The carbon dioxide content was 34.5 volumes per cent.

Clinical Impression: The patient had a malformation which caused inadequate pulmonary blood flow, but the nature of this malformation was not clear.

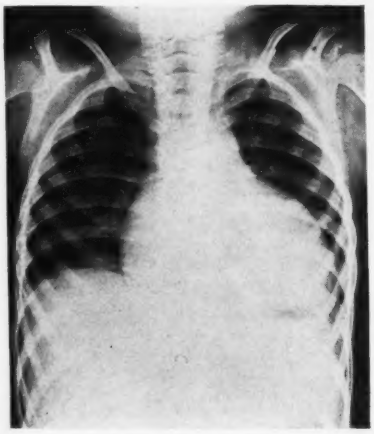

FIG. 5.—Anterior-posterior view of the chest. Case 2.

Course: Because of the enlarged heart and liver, the patient was given digitalis. While on this medication, his liver decreased slightly in size, his cyanosis lessened, and his exercise tolerance increased so that by the age of 5 years he could walk four blocks slowly and climb one flight of stairs. His heart, however, continued to enlarge. The cardiothoracic ratio in January, 1947, measured 68 per cent. The heart sounds remained faint; the gallop rhythm and systolic murmur persisted. His blood pressure was 98/84 mm. of Hg. The arm-to-lips circulation time determined with fluorescein was 12 seconds. (The upper limits of normal for his size is 9 seconds.) In January, 1948, at the age of 5 years, he returned for additional diagnostic studies.

Angiocardiogram in the anteroposterior view showed that the contrast medium entered through the superior vena cava into the large right auricle and then dispersed throughout the entire heart. The contrast medium extended almost to the margins of the cardiac silhouette, indicating that the

walls were thin. The Diodrast lingered for an abnormally long time in the right side of the heart. The pulmonary vascular bed opacified slowly and in a subnormal amount. The aorta was not visualized in the anteroposterior view. In the films taken with the patient lying on his left side, some of the Diodrast passed from the large right auricle directly into the left auricle, indicating a defect in the auricular septum. The left auricle emptied the dye promptly into the left ventricle; then the aorta filled. (See fig. 6.)

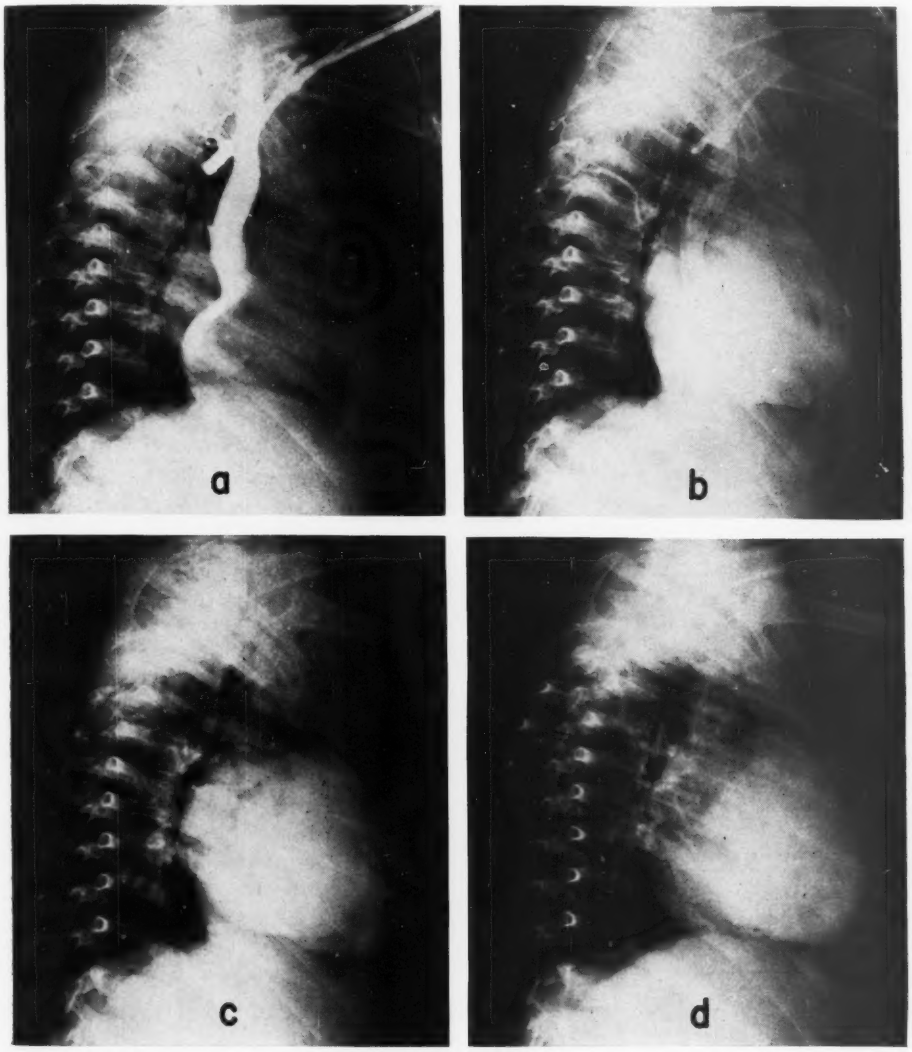

FIG. 6.—Angiocardiogram, lateral position. Case 2. *a*. Film taken 1 sec. after injection shows Diodrast entering right auricle through superior vena cava. *b*. Two seconds. Dye has filled the enlarged right auricle and is visible in the left auricle. *c*. Four seconds. The contrast medium is dispersed throughout the right auricle and right ventricle and is visible in the pulmonary arteries. The aorta is opacified. *d*. Seven seconds. Dye has disappeared from the left side of the heart and the aorta but still lingers in the right side of the heart.

Cardiac Catheterization: The oxygen content of

the superior vena cava was 16.1 volumes per cent; of the right auricle 17.5 volumes per cent; and of what was thought to be the right ventricle, 17.8 volumes per cent. The pressure in the right auricle was 8/1 mm. of Hg. and in the latter chamber, 21/7 mm. of Hg. The pulmonary artery could not be entered. The catheter tip passed into two chambers, the oxygen contents of which were higher than those of the right side of the heart. These chambers were interpreted as the left auricle (oxygen content 21.8 volumes per cent; pressure 8/2 mm. of Hg.) and the left ventricle (oxygen content 21.5 volumes per cent; pressure 48/12 mm. of Hg.). The oxygen content of the femoral artery was 20.2 volumes per cent, and the oxygen capacity 30.6 volumes per cent, giving an arterial oxygen saturation of 66 per cent. The pulmonary blood flow was markedly reduced; it was only 1790 cc. per square meter of body surface per minute as compared with a systemic blood flow of 4350 cc./sq. M./min. The effective pulmonary flow was calculated to be 1320 cc./sq. M./min. Although there was some shunting of oxygenated blood into the right auricle, the overall intracardiac shunt was from right to left and was of the magnitude of 2560 cc./sq.M/min.

On the basis of these tests it was believed that the patient had a tetralogy of Fallot and an auricular septal defect, and probably could be benefited by a Blalock-Taussig operation. On January 12, 1948 an anastomosis was performed between the end of the right subclavian artery and the side of the right pulmonary artery. Three times during the operation the heart stopped beating; shortly after the chest was closed, the heart again stopped and could not be revived.

Postmortem Examination: Autopsy No. 21012, performed by Dr. Payne. On opening the thoracic cavity, the right auricle and right ventricle were seen to be so dilated that the heart filled most of the left chest and extended far into the right chest. As in the first case the left ventricle was normal in size and was entirely concealed behind the huge right ventricle.

The heart weighed 100 grams (normal approximately 95 grams); thus there was little or no hypertrophy. The pericardial sac was normal. The venous return was normal. There was a poorly developed eustachian valve, and the orifice of the coronary sinus was atretic. The right auricle was hypertrophied as well as dilated. The foramen ovale was patent, measuring 1 cm. in diameter. Although the foramen ovale was guarded by a valve, the tremendous dilatation of the right auricle caused the valve to be incompetent.

The tricuspid valve was greatly malformed (fig. 7). It extended down into the right ventricle and was fused in places with the endocardium and in other places closely bound to it by short chordae tendineae and small papillary muscles. In the region of the infundibulum of the right ventricle, it formed a redundant membrane which divided the right ventricle into two parts: a small outflow chamber which emptied into the pulmonary artery, and a much larger chamber continuous with the right auricle through the unprotected tricuspid valve ring. The latter measured 9 cm. in circumference.

The individual leaflets of the tricuspid valve were difficult to identify. On the septal portion of the auriculoventricular ring, there was no valve leaflet distinguishable from the smooth endocardial surface. From the remainder of the auriculoventricular ring, there arose a large leaflet which extended into the ventricular cavity and was closely attached to its wall. The leaflet blended distally with the septal endocardium except in the region of the infundibulum of the right ventricle, where it presented a partially free margin for a distance of 6 cm. In this portion of the valve there was an opening which measured 1.5 cm. in diameter and was situated 1 cm. from the free margin. The edges of this opening were attached to the ventricle wall by short chordae tendineae and tended to overlap. Communication between the two chambers of the right ventricle was through the opening in the valve leaflet itself or through the orifice formed by the free margin of the valve and the ventricular septum. Both of these openings would have closed during ventricular systole. The wall of the right ventricle above the abnormal valve was exceedingly thin; in some places it measured not more than 1 mm. in thickness (fig. 8). Microscopically the muscle fibers were normal in appearance but reduced in number. In the region of the infundibulum of the right ventricle, however, the myocardium was 3 mm. in thickness and microscopically was normal.

The pulmonary valve was entirely normal; the valve ring measured 2.5 cm. in circumference. The pulmonary trunk was normal. The right subclavian artery was anastomosed surgically to the right pulmonary artery. The ductus arteriosus was obliterated. The ventricular septum, the left auricle and left ventricle, the mitral and aortic valves, and the aorta were normal. The coronary arteries were normal. The thebesian veins were prominent. There was no passive congestion of the viscera.

Anatomic Diagnosis: Congenital malformation of the heart. Ebstein's anomaly of tricuspid valve. Patent foramen ovale. Congenital hypoplasia of right ventricular myocardium. Hypertrophy and dilatation of right auricle. Extreme dilation of right ventricle. Persistent eustachian valve, poorly developed. Atretic orifice of coronary sinus. Large Thebesian veins. Surgical anastomosis of right subclavian to right pulmonary artery.

Case 3.—C. T. (HLH No. A 46196), a 16 year old white girl, was seen in the Cardiac Clinic in February, 1946, at the age of 14 years.

Past History and Present Illness: She was born with scoliosis and was cyanotic at birth. After the first few days the cyanosis disappeared. She was able to run and play until the age of 3 years. At this time the cyanosis reappeared; it was variable at first but gradually became constant. From the age of 6 years she received digitalis for "rapid heart action." Her exercise capacity became progressively more limited. Until the age of 11 dyspnea was very slight; thereafter, it steadily increased although it never became as marked as the cyanosis. As her dyspnea increased, she developed the habit of occasionally squatting to rest.

Physical Examination: Temperature 37 C.; pulse 100 per minute; respirations 24 per minute. She was a moderately well developed and well nourished

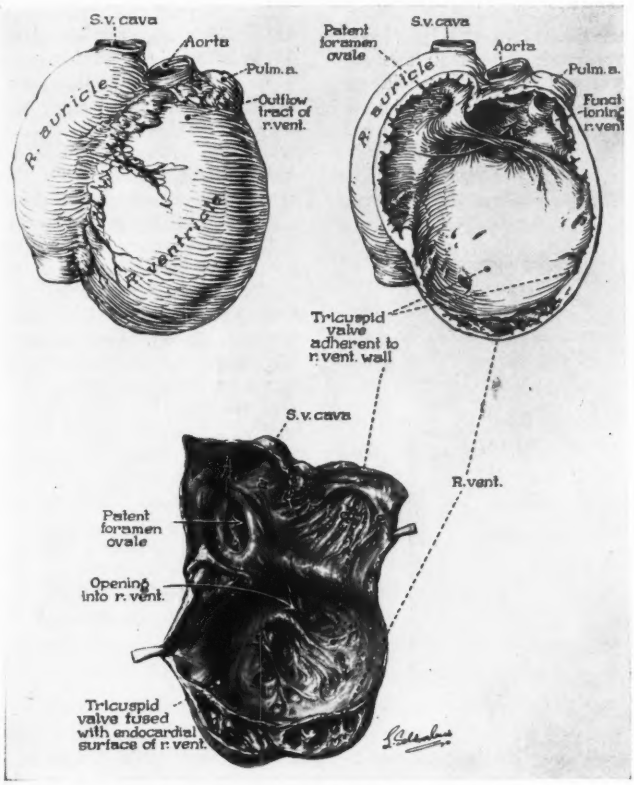

FIG. 7. Ebstein's anomaly of the heart. Case 2. Note similarity to figure 3.

FIG. 8.—Section through tricuspid valve ring. Case 2. Note extreme thinness of right ventricular wall, *V*, as compared with right auricular wall, *A*. The valve leaflet is not present in this section.

girl with a severe S-shaped dorso-lumbar scoliosis and marked chest deformity. Cyanosis was moderately intense. There was slight clubbing of the fingers and toes. The heart was enlarged. The point of maximal impulse was beyond the posterior axillary line. The first heart sound was obliterated by a loud, rasping, systolic murmur which was audible all over the precordium. It was especially well heard in the second intercostal space at the left sternal border, in the fourth and fifth intercostal spaces, and in the posterior axillary line. The liver was palpable at the costal margin but was not pulsating. There was no edema. The remainder of the examination was negative.

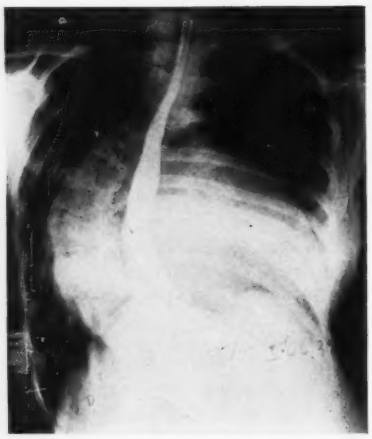

FIG. 9.—Anterior-posterior view of chest. Case 3.

Laboratory Findings: Both teleoroentgenogram and fluoroscopy revealed a tremendously enlarged heart which filled the left chest (fig. 9). There was an abrupt angulation at the base and an absence of fullness in the pulmonary conus region. The pulmonary arteries were not enlarged, and there were no expansile pulsations visible in them. The lung fields were exceptionally clear. With barium swallow there was seen a left aortic arch and no evidence of left auricular enlargement. The cardiothoracic ratio was 66 per cent.

The electrocardiogram showed right axis deviation, first degree heart block, and prolongation of intraventricular conduction time suggesting right bundle branch block. The P waves were high and peaked. T_2 and T_3 were inverted. Unipolar precordial leads were not obtained. The red blood cell count was 7.31 million per cu. mm.; the hemoglobin level was 20 Gm.; the hematocrit reading was 75. Analysis of the arterial blood sample revealed an oxygen content of 21.7 volumes per cent, an oxygen capacity of 34.1 volumes per cent, and an arterial oxygen saturation of 64 per cent. The carbon dioxide content of the arterial blood was 31.4 volumes per cent.

Clinical Impression: It was believed that the primary difficulty was an inadequate pulmonary blood flow, but the great cardiac enlargement and the scoliosis were considered contraindications to a Blalock-Taussig operation.

Course: In 1948, when seen elsewhere, she was thought to have a tetralogy of Fallot. At that time a gallop rhythm was heard, and her blood pressure was found to be 130/110 mm. of Hg. Because she was extremely anxious for operation, it was attempted. Due to technical difficulties it was impossible to complete the anastomosis. Two weeks later, following a stormy postoperative course complicated by thrombophlebitis and cardiac failure, she died.

Postmortem Examination:* Autopsy showed that the right auricle and the right ventricle were extremely dilated. The anomalous tricuspid valve formed an apron-like structure, which extended so far down into the cavity of the right ventricle that the functional portion of the right ventricle was very small, and only the outflow tract of the ventricle was relatively normal in size. The posterior leaflet of the tricuspid valve was fused to a considerable extent with the endocardium. The anterior leaflet in its inferior margin was fixed to the endocardium. The medial leaflet was small and could not be separated from the posterior leaflet. The actual ostium of the distorted tricuspid valve measured 8 cm. in circumference. The myocardium of the right ventricle proximal to the valve was exceedingly thin; it measured between 1 mm. and 2 mm. in thickness. The myocardium distal to the valve was of normal thickness. The foramen ovale was widely patent. The ventricular septum was intact. The pulmonary valve and pulmonary artery, the left auricle and left ventricle, the mitral and aortic valves, and the aorta were normal. There was passive hyperemia of the abdominal viscera. An adherent thrombus filled the main iliac veins and extended into the inferior vena cava. There was marked scoliosis.

Anatomic Diagnosis: Congenital malformation of the heart. Ebstein's anomaly of tricuspid valve. Patent foramen ovale. Congenital hypoplasia of right ventricular myocardium. Extreme dilatation of right auricle and right ventricle. Scoliosis.

ANALYSIS OF THE PATHOLOGIC, CLINICAL, AND LABORATORY FINDINGS

The anomaly of the tricuspid valve described in these 3 cases is similar to that recorded by Ebstein.[1] In each instance the foramen ovale was patent, as it was in Ebstein's original case and in two-thirds of those subsequently reported.[1, 3–5, 7, 11–15, 18] In association with the

* We are indebted to Dr. K. Terplan for this report.

malformation of the tricuspid valve, in all 3 hearts there was a congenital hypoplasia of the right ventricular myocardium above the malformed valve. The myocardium of the chamber of the right ventricle against which the tricuspid valve was plastered was extremely thin, whereas the ventricular wall of the outflow chamber was of normal thickness. It seems quite unlikely that dilatation alone could have caused this unusual thinness of the myocardium. Thinness of the right ventricular wall proximal to the valve has been noted in nearly all the recorded cases.[1–5, 7–15, 18] The case previously reported by Taussig[19] was re-examined and in this instance, too, the myocardium in the upper portion of the right ventricle was extremely thin. In 2 cases[9, 15] there was an area of localized out-pouching where the wall was exceedingly thin. These areas were considered to be developmental defects. It seems probable, therefore, that hypoplasia of the myocardium of the right ventricle proximal to the malformed tricuspid valve is an integral part of the malformation.

This malformation of both the tricuspid valve and the wall of the right ventricle appears to be due to a developmental defect in the formation of the tricuspid valve and of the myocardium of the right ventricle. Streeter[20] has shown that embryologically the myocardium arises from a specialized part of the visceral coelomic wall and is separated from the partially distended endocardium of the primitive heart by the myoendocardial space, which extends throughout the length of the heart tube. This space is filled with a homogeneous transparent jelly, the cardiac jelly. As the myocardium develops, the myoendocardial space gradually disappears except at strategic sites, where it persists as the so-called endocardial cushions from which the tricuspid and other valves are formed. It is thus possible that any defect in the visceral coelomic wall in the region where the right ventricle is to develop could not only cause defective development of the right ventricular myocardium but, by distortion of the position of the persisting primitive myoendocardial space, could cause a malformation of the tricuspid valve.

In these hearts the tricuspid ring is unprotected by a valve, and at first sight it appears that there must have been extreme tricuspid insufficiency. It has frequently been stated in the literature that the valve is insufficient; indeed, "congenital tricuspid insufficiency" has been used as a synonym for Ebstein's anomaly. Nevertheless, it is a striking fact that in our Case 2 and also in the case reported by Taussig[19] there was no chronic passive congestion of the viscera at autopsy. Moreover, in the first case there was only moderate chronic passive congestion of the liver and pancreas; there was not the intense damage that would have been expected had a tricuspid insufficiency existed over a period of years. Only in Case 3 was there passive hyperemia of the abdominal viscera; this was in all probability a terminal event.

The lack of chronic passive congestion and the absence of clinical evidence of tricuspid insufficiency in the 3 other cases were due primarily to the fact that, although the tricuspid ring was unprotected by a valve, the anomalous valve was so arranged that it was competent. The opening between the two chambers at the margin of the redundant valve was closed during ventricular systole. Although the upper chamber may have been unable to empty itself completely with each contraction, the thinness of the wall of the ventricular portion permitted it to serve as a distensible reservoir and lessened the manifestations of right heart failure. Furthermore, the patency of the foramen ovale acted as an "escape valve" and enabled blood to be shunted into the left auricle.

It seems probable that there were two factors involved in the dilatation and hypertrophy of the right auricle proper: first, the opening from the proximal chamber into the outflow chamber was considerably smaller than that of a normal tricuspid valve and thus constituted a functional tricuspid stenosis; second, the outflow chamber, which was smaller than a normal ventricle, was too small to receive all the blood contained in the upper chamber, so that the right auricle was unable to empty itself completely.

Because of the anomalous position of the tricuspid valve, this malformation primarily alters the efficiency of the right heart. The

inefficiency is more readily apparent when one considers how the heart functions when part of the right ventricle is included in the right auricle.

Venous blood is returned in the normal fashion to the right auricle. Auricular systole directs the blood through the proximal portion of the right ventricle, which is in free communication with the right auricle. The direction of the blood through the malformed tricuspid valve into the distal portion of the right ventricle is, however, difficult. The effectiveness of the auricular contraction is lessened by the dilated upper part of the right ventricle, which during auricular systole is in diastole. The tricuspid orifice is relatively small and, furthermore, the distal chamber is too small to receive all the blood from the large proximal chamber. Consequently, the upper chamber is unable to empty itself completely. Although the expulsion of blood may at first be relatively adequate, gradually the volume of blood remaining in this chamber increases. It follows that the ability of the chamber to empty itself progressively lessens. This chamber gradually enlarges, and the pressure increases. The greater the proportion of the right ventricle above the tricuspid valve, the smaller is the distal chamber; as a consequence, the greater is the difficulty of the proximal chamber in propelling blood forward, and the greater is its enlargement.

If the foramen ovale is not completely sealed, as the pressure within the right auricle increases, the valve is forced open, and venous blood is shunted into the left auricle. As the pressure continues to rise, the foramen ovale is constantly held open, and the right-to-left shunt becomes persistent. If the right auricle becomes so distended that the foramen ovale is stretched wide open, there is in effect a gross defect in the auricular septum.

During ventricular systole the misplaced tricuspid leaflets close the opening between the lower and upper chambers, and the distal chamber sends the blood to the lungs. Inasmuch as the volume of blood contained in the lower chamber is less than normal, the lungs receive an inadequate supply of blood for oxygenation. The pulmonary circulation is further diminished by the shunt through the foramen ovale. Although the musculature of the "auricularized" right ventricle is thin and cannot exert much force, it seems probable that it too contracts during ventricular systole and sends the blood against the closed tricuspid valve, against the walls of the auricle, and possibly through the foramen ovale to the left auricle.

The venous blood shunted from the right auricle to the left auricle is mixed with the fully oxygenated blood which is returned from the lungs to the left auricle. This admixture of venous and arterial blood reaches the systemic circulation via the left ventricle and the aorta, and when the venous-arterial shunt is of sufficiently large volume, cyanosis results. If the foramen ovale is closed and there is no defect of the auricular septum, there is no right-to-left shunt; consequently, there is no cyanosis. Under such circumstances the course of the circulation, except for the delay in expulsion of blood from the proximal chamber, is normal.

An analysis of these cases and of those in the literature bears out the theory that the presence or absence of cyanosis is related to the structure of the auricular septum. The foramen ovale was patent in fifteen[1, 3–5, 7, 11–15, 18] of the 22 cases reported. Cyanosis was present in all 11 of these 15 cases in which clinical information was given. Another patient who was cyanotic had a gross defect in the auricular septum; this would similarly permit a right-to-left shunt.[10] One patient had only probe patency of the foramen ovale and was not cyanotic.[16] In 3 patients the foramen ovale was closed. In one of these[9] there was no cyanosis. In the second[8] cyanosis was noted only "at times" on the third day before death and was associated with terminal heart failure. In the third[7] no clinical history was given. In the remaining 2 cases[6, 17] there was no information given concerning cyanosis or the structure of the foramen ovale. In each of our cases the foramen ovale was patent and all 3 patients showed persistent cyanosis. In the case reported by Taussig,[19] although the foramen ovale was patent, the patient became cyanotic only during the periods of paroxysmal tachycardia and terminally when in heart failure. In this case it is noteworthy that there was less disproportion

between the sizes of the chambers proximal and distal to the malformed tricuspid valve than in the preceding three cases, and consequently the pressure in the right auricle was in all probability but slightly increased.

The malformation may be compatible with life for varying lengths of time. Marxsen's patient lived to be 61 years old,[2] and Malan's lived to the age of 60 years.[6] On the other hand, one child lived for only eight months,[15] and several others[4, 7] died in early childhood. The average age at death was 24 years. The variation in longevity and also in symptomatology is in all probability due to the relative proportions of the right ventricle above and below the anomalous tricuspid valve. If the distal chamber is approximately of normal size, the alteration of the course of circulation is slight, and the symptoms are correspondingly few. On the contrary, when the tricuspid valve is displaced so far downward into the cavity of the right ventricle that the distal chamber is much reduced in size and the greater portion of the right ventricle is proximal to the valve, then the right heart becomes extremely inefficient. Under such conditions the cardiac enlargement is great and progressive, symptoms appear at an early age, and the duration of life is relatively short.

The clinical and laboratory findings in patients with Ebstein's anomaly of the tricuspid valve are explicable on the basis of the altered function of the right side of the heart. The delay in the onset of the cyanosis is dependent on the physiologic closure of the foramen ovale shortly after birth. A right-to-left shunt is thus prevented until the pressure in the right auricle has increased to the level where the foramen ovale is forced open. Thereafter, when a sufficient volume of unoxygenated blood is shunted into the systemic circulation, cyanosis becomes apparent. The tremendous cardiac enlargement is the result of the difficulty in the expulsion of blood from the right auricle. The muffled quality of the heart sounds and the gallop rhythm doubtless reflect the poor functioning of the dilated right side of the heart. The origin of the murmurs, however, is not clear. There are a number of possible factors. The systolic murmur may have been caused by the passage of blood from the right to the left auricle and perhaps also by the regurgitation of a small amount of blood from the lower to the upper chamber through the fenestrations in the malformed valve. The loud systolic murmur heard posteriorly in Case 1 was possibly caused by blood coursing over the enlarged noderator band. The diastolic nurmur noted in addition to the systolic murmur in Case 1 and in some of the previously reported cases[1, 2, 5, 10, 16] may have been associated with the abnormal currents of blood within the chamber proximal to the malformed valve as with each cardiac cycle the auricular and the ventricular portions contracted independently.

There was electrocardiographic evidence of prolonged auriculoventricular conduction time in all 3 patients, and in 2 there was a right bundle branch block. In Case 3 there was right axis deviation and evidence of delayed intraventricular conduction suggesting a right bundle branch block. Unipolar precordial leads were not obtained on this patient; hence, no definite statement can be made as to the presence or absence of a bundle branch block. In each of the 3 cases[12, 18, 19] recorded in the literature in which electrocardiograms were illustrated, there appeared to be prolongation of auriculoventricular and intraventricular conduction time. Bauer's patient[16] had a right bundle branch block. Conduction defects are not surprising in view of the tremendous dilatation and thinning of the right auricle and proximal portion of the right ventricle.

The abnormally long circulation time is due to the delay in the expulsion of blood from the large upper chamber. This causes the test solution to linger there before it circulates through the lungs and then reaches the systemic circulation. Although the foramen oval be patent, it has been our clinical experience that rarely is sufficient test material shunted from right to left to give a short circulation time.

The fluoroscopic findings of abnormally clear lung fields and absence of pulsations of the pulmonary arteries are caused by the reduced pulmonary blood flow. It seems reasonable to believe that weak pulsations of the right heart are characteristic of this malformation and will be found, if carefully searched for, in all such

patients. In Case 1 of this report and in Bauer's patient,[16] a decreased amplitude of cardiac pulsations was observed.

The condition leads to progressive cardiac enlargement. In our cases prior to death the cardiothoracic ratio ranged from 66 per cent to 77 per cent, and in Bauer's patient[16] it eventually reached 84 per cent. It is worthy of note that in both our first two patients the left ventricle as well as right ventricle was thought to be enlarged because in the left anterior-oblique position the left ventricle overlapped the spine, even upon extreme rotation. Autopsy, however, showed that all the enlargement was right auricle and right ventricle. Thus it is evident that the right side of the heart can enlarge so greatly that it displaces the left ventricle far posteriorly and causes it to overlap the spine even when the patient is rotated almost into the lateral position.

The findings on angiocardiography reflect the inefficient action of the right heart and the patency of the foramen ovale. The Diodrast was pooled for an abnormally long time in the large proximal chamber. Although the dye which reached the functioning portion of the right ventricle was promptly expelled into the lungs, the lungs never opacified normally because only a small amount of contrast medium was delivered by each ventricular contraction. The concentration of Diodrast in the aorta after some of the dye had been shunted through the foramen ovale from the right auricle into the left was much less dense than that seen with early visualization of an overriding aorta such as occurs in the tetralogy of Fallot.[21]

The catheterization findings of a reduced pulmonary blood flow and a right-to-left shunt are due to the shunting of unoxygenated blood away from the lungs through the patent foramen ovale into the left side of the heart. Although safely performed in one of our patients (Case 2) we feel that cardiac catheterization in patients with Ebstein's anomaly is not without danger. Because of the common occurrence of conduction disturbances, there is the possibility of initiating an arrhythmia which might prove fatal. Furthermore, there is the theoretical danger of entangling the catheter in the delicate, basket-like membrane or its fenestrations. Finally, it is conceivable that the catheter might perforate the exceedingly thin-walled ventricular portion of the upper chamber, especially in a patient with a localized aneurysmal dilatation.

The Clinical Syndrome

The correlation of these clinical, laboratory, and pathological findings reveals that a distinct picture is produced when Ebstein's malformation of the tricuspid valve is combined with patency of the foramen ovale or with a gross defect in the auricular septum.

History: The onset of cyanosis is usually delayed. If present at birth, the cyanosis promptly lessens or disappears but returns at a later age. It is transient at first and insidiously becomes persistent. The cyanosis is more marked than the dyspnea, which is quite mild. There is easy fatigability. Although the patients tire quickly and often have to stop to rest, squatting is not a common habit.

Physical Findings: Outstanding features, in addition to the cyanosis and slight clubbing, are the enlarged heart, the left-sided chest deformity, the distant or muffled heart sounds, and often a gallop rhythm. There is a systolic murmur maximal at the left sternal border in the third intercostal space but audible all over the precordium. There may also be a diastolic murmur over the sternum, which may give the impression of a friction rub. The pulse pressure is narrow. The liver is slightly to moderately enlarged, but there are no pulsations palpable at its margin unless with terminal failure, and there are no other signs of tricuspid insufficiency.

Laboratory Findings: There is arterial oxygen unsaturation and compensatory polycythemia. The circulation time is prolonged. The electrocardiogram usually shows right bundle branch block and prolonged A-V conduction time. Fluoroscopy in the anteroposterior view usually shows a greatly enlarged heart with diminished pulsations. The tremendous size of the right auricle and right ventricle causes enlargement both anteriorly and posteriorly in the oblique views. There is no fullness in the the region of the pulmonary conus. A pulmonary artery of normal size is seen bilaterally,

but no expansile pulsations are visible therein. The lung fields are abnormally clear. The esophagram upon barium swallow is normal.

Angiocardiogram shows a large right auricle and then an early but less dense concentration of the contrast medium in the right ventricle. The entire cardiac shadow visible in the anterior-posterior view appears to be formed by the right auricle and the right ventricle. The contrast medium extends nearly to the margin of the cardiac silhouette, indicating that the chambers are quite thin-walled. The Diodrast lingers for several seconds in the right auricle and the "auricularized" right ventricle, whereas the dye is quickly expelled from the functioning right ventricle into the pulmonary arteries. The opacification of the lungs is less than normal. A small amount of the contrast medium may be seen to pass from the right auricle into the left auricle, the left ventricle, and into the aorta. Cardiac catheterization shows a reduced pulmonary blood flow and an overall right-to-left shunt between the auricles. The pressure in the right ventricle distal to the valve is within normal limits.

Differential Diagnosis: This malformation is to be differentiated from other conditions in which there is cyanosis and an inadequate pulmonary blood flow. The most important malformations from which to differentiate it are the tetralogy of Fallot and valvular pulmonary stenosis.

The chief features which differentiate this malformation from the tetralogy of Fallot are the delayed onset of cyanosis, the absence of paroxysmal dyspnea and of squatting to rest, the cardiac enlargement, the diastolic murmur, the long circulation time, the electrocardiographic evidence of first degree heart block and of bundle branch block, and finally the angiocardiographic evidence of the enormous size and slow emptying of the right auricle.

Ebstein's malformation may even more closely resemble an isolated valvular pulmonic stenosis with patency of the foramen ovale and no defect in the ventricular septum than it does a tetralogy of Fallot. In a subsequent publication[22] the clinical and laboratory findings of this type of pulmonic stenosis will be presented and the differential diagnosis discussed.

Summary

The clinical, laboratory, and pathologic findings in 3 cases of Ebstein's anomaly of the heart have been presented. This brings the total number of cases in the literature to 26. A correlation of the findings in the cases discussed in this paper and of those collected from the literature has demonstrated that this malformation is sufficiently characteristic to constitute a clinical syndrome which may be correctly diagnosed during life.

In this malformation the displaced tricuspid valve divides the right ventricle into two parts and thereby causes the proximal portion to be continuous with the cavity of the right auricle. The anomalous valve is so arranged, however, that it is competent. The myocardium of the right ventricle proximal to the malformed tricuspid valve is congenitally thin. The primary effect of the anomaly is to reduce the efficiency of the right heart. As the upper chamber cannot empty itself completely, it enlarges progressively. If the foramen ovale is incompletely sealed, it is opened, and venous blood is shunted from the right auricle into the left auricle and thence into the systemic circulation. The lower chamber, which receives less than the normal volume of blood, delivers an inadequate amount of blood to the lungs for oxygenation.

The outstanding clinical manifestations are the delayed and insidious onset of cyanosis, which is out of proportion to the mild dyspnea; the easy fatigability, and the infrequency of squatting to rest when tired. Physical examination shows excessive right heart enlargement, poor heart sounds usually associated only with a systolic murmur but sometimes also with a diastolic murmur and often with a gallop rhythm, and absence of signs of tricuspid insufficiency. The chief laboratory findings are the x-ray evidence of progressive cardiac enlargement and a concave pulmonary conus region and abnormally clear lung fields, the fluoroscopic visualization of diminished pulsations of the right side of the heart and absence of pulsations in the pulmonary arteries, the electrocardiographic signs of delayed A-V conduction and of right bundle branch block, the prolonged circulation time, the oxygen unsatu-

ration of the arterial blood, and the compensatory polycythemia. Angiocardiography is helpful in confirming the diagnosis and in this malformation is safer than is cardiac catheterization.

It is important to distinguish this malformation, which cannot be helped by present forms of surgery, from those such as the tetralogy of Fallot which are amenable to operation. The differential diagnosis is discussed.

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A Comparison of Cardiac Output Determined by the Fick Procedure and a Direct Method Using the Rotameter

By ROBERT D. SEELY, M.D., WILLIAM E. NERLICH, M.D., AND DONALD E. GREGG, PH.D., M.D.

Experiments were performed on the anesthetized dog to determine the accuracy of the widely used Fick procedure. Cardiac output values, recorded by an optical rotameter, served as a reliable standard for comparison. Under the conditions of these experiments, comparisons showed excellent agreement. The average variation between the two series of the measurements was ±5 per cent. Twelve of thirteen comparisons agreed within less than ±8 per cent. This small deviation was within the range of error which might have existed on the basis of known technical inaccuracies.

THE FICK procedure has gained acceptance as one of the most reliable of the many technics for quantitating cardiac output. The accuracy of most other methods has been established by comparison with it, and since the advent of right heart catheterization it has become an important tool in clinical research. Such reliance, however, as has been placed upon the Fick procedure does not seem wholly justified, since it is an indirect method and has never been satisfactorily checked against a standard of established accuracy. Data from the experiments of Bohr and Henriques[1] in 1897 show that in dogs the Fick method gives values far too high when compared with a direct technic (stromuhr in the aorta). While these experiments are undoubtedly crude by present day standards, they have never been repeated; and the absolute accuracy of the Fick method has remained a question. Accordingly, in the present investigation, experiments were performed in the anesthetized dog in which the cardiac output was determined simultaneously by the Fick procedure and an optical rotameter method. The rotameter could be safely used as a standard of reference, since it has been shown that this device measures blood flow directly with a high degree of accuracy.

METHODS

Flow measurements were made simultaneously by the Fick procedure and rotameter over a six-minute period in open-chest dogs which were anesthetized with Nembutal (20–30 mg. per Kg., intravenously) or barbital (200 mg. per Kg., intravenously) following morphine (30 mg.).

For the Fick procedure, oxygen consumption was measured with a Benedict-Roth metabolism apparatus (Collins), which was modified for use in open-chest dogs after the plan of Harris and Matlock[2] (see fig. 1). To improve the accuracy with which the oxygen slope could be read, the sensitivity of the apparatus was increased by means of a pulley system so that 1.0 mm. deflection equalled 8.33 cc. A rubber catheter was inserted through a tracheal incision and tied securely, and the spirometer containing 100 per cent oxygen was attached to the catheter ten minutes or more before a test period began. To test for leaks, at the end of each experiment the apparatus was run for four to six minutes with the dead dog in the circuit.

Arterial blood samples were obtained by puncturing a rubber vial cap which sealed the vertical limb of a glass T-tube in the carotid artery. Mixed venous samples were taken directly from the outflow side of the rotameter which measured flow through the pulmonary artery. Samples were drawn manually in oiled syringes containing enough heparin to fill the terminal dead space. They were taken simultaneously and continuously at 1.0 cc. per minute during the six minutes in which oxygen consumption was measured. Immediately after withdrawal, the syringes were capped and placed in ice water, and within two to three hours the oxygen content of each sample was determined in duplicate by the manometric method of Van Slyke and Neill.[3] Blood from each dog was also analyzed for oxygen capacity.

As a standard of reference for the Fick procedure, the cardiac output was determined directly by measuring blood flow through the pulmonary artery with an optical rotameter. This method, described in a previous communication,[4] avoids the error inherent in other direct procedures which fail to measure coronary flow (flow meters in aorta and venae cavae). Briefly, the pulmonary artery was exposed, dissected free, and a specially devised cannula was inserted into the artery. During cannulation, hemorrhage was avoided by diverting the flow through a

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temporary shunt or by a fibrillation-defibrillation technic which permitted a temporary cessation of the circulation. After insertion of the cannula, the rotameter was attached to it. The output of the right heart then passed from the pulmonary artery through the rotameter and was distributed to the right and left lungs. This circuit permitted continuous optical recording of total cardiac output. Heparin (10 mg./Kg.) was used as anticoagulant with the rotameter. In order to obtain different levels of flow, varying amounts of blood (50–200 cc.) and/or epinephrine (1:5000 or 1:10,000) were administered intravenously during some of the test periods. After each experiment, the rotameter was calibrated with the dog's own blood. Mean flow for each minute was calculated by planimetric integration of the area under the recorded flow curve, and the average flow per minute for the six-minute test period was compared with that obtained by the Fick procedure.

In addition, early in this investigation, several experiments were performed in which cardiac output determined by the Fick procedure was compared with right heart input, determined by the method of Gregg and Shipley.[5] Blood was collected from the venae cavae and after passage through a rotameter was returned to the right atrium. Coronary venous return, of course, was not measured. Rotameter values were corrected, however, to account for coronary flow, according to the data of Eckenhoff and associates.[6] In these experiments, the chest was closed by placing sponge-rubber pads between the skin and the chest cage, and an unmodified, ordinary Benedict-Roth spirometer was used to measure oxygen consumption. Collection and analysis of blood samples were carried out as described above, except that mixed venous samples were obtained from a catheter placed in the pulmonary artery.*

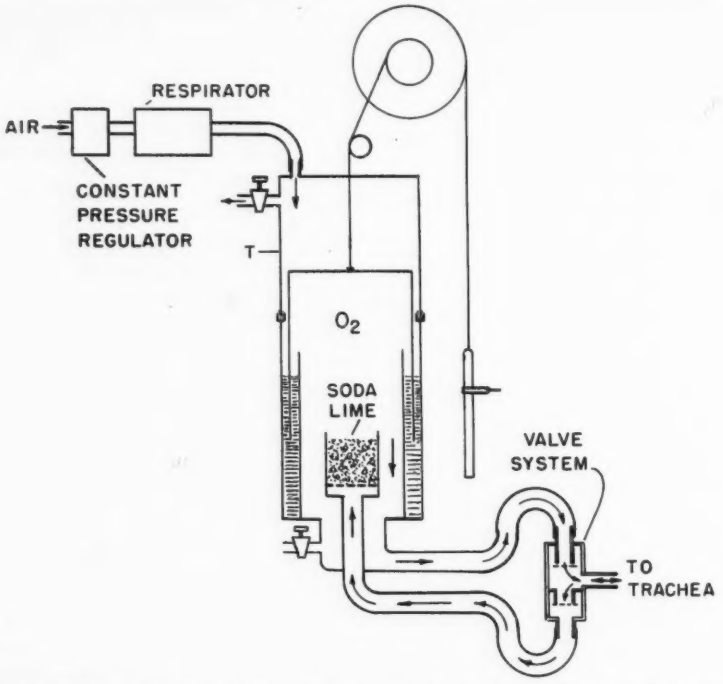

FIG. 1.—Diagram of basal metabolism apparatus used as spirometer and artificial respirator. Tank *T* is added to enclose spirometer bell. Positive pressure delivered intermittently to *T* inflates lungs, deflation occurring when pressure is dissipated through regulated leak valve. Bell is undercounterbalanced to assist deflation. External system replaces inside flutter valves.

Combining the Fick procedure with direct technics proved difficult, and the number of successful experi-

* In both open and closed-chest experiments, venous samples were obtained from the pulmonary artery, which site has been shown to be optimal in dogs for complete mixing.[7] Data collected in the preparatory stages of the present work confirmed this fact. In one typical experiment, four samples drawn simultaneously by catheters from the right ventricle conus, and two sites in the left pulmonary artery showed oxygen contents, respectively, of 9.42, 9.63, 9.72, and 9.72 volumes per cent.

ments was, therefore, limited. Of thirty-three experiments begun, eighteen were completed. Of these, eight were discarded because leaks in the spirometer system could be demonstrated or duplicate blood oxygen content determinations did not check closely enough. The remainder, thirteen comparisons in 10 dogs, forms the basis for this report.

the direct methods are expressed as per cent deviation of the former from the latter. The average variation between the two series of measurements is ±5 per cent. It can be seen that eight of the thirteen comparisons agree within 3 per cent, twelve of the thirteen within

TABLE 1.—*Comparison of Cardiac Output by Fick and Rotameter Methods**

Experiment	Weight	Mean B. P.	Fick						Rot. Flow	% Diff.
			O_2 Consumption	O_2 Capacity	Art. O_2	Ven. O_2	A-V Diff.	Flow		
	Kg.	*mm. Hg*	*cc./min.*	*Vol. %*	*Vol. %*	*Vol. %*	*Vol. %*	*cc./min.*	*cc./min.*	
1. (2/21/49)	10.2	78	83.4	21.31	20.47	8.11	12.40	672	635	+6
					20.51	8.08			(668)	(+1)
2. (2/23/49)	10	85	78	19.25	15.84	7.66	8.17	955	845	+13
					15.84	7.68			(890)	(+8)
3. (2/24/49)	9.5	85	63.2	19.68	11.22	6.85	4.38	1443	1390	+4
					11.23	6.84			(1463)	(−1)
a.		75–100	81.2	—	15.38	8.09	7.31	1110	1080	+3
4. (8/30/49)	11				15.39	8.06				
b.		92	84	—	14.55	6.25	8.30	1012	1090	−7
					14.51	6.20				
5. (9/1/49)	12	123	21	18.22	15.58	13.62	2.01	1045	895	+17
					15.60	13.55				
a.		95	77	16.75	15.70	7.84	7.83	984	915	+8
6. (10/12/49)	—				15.58	7.79				
b.		60–160	81	19.52	16.05	8.92	7.14	1132	1235	−8
					16.05	8.91				
7. (11/8/49)	15	95	94	22.00	17.31	6.35	10.94	861	873	−2
					17.25	6.34				
a.		87	82		19.69	12.10	7.62	1080	1060	+1
8. (11/15/49)	12			23.32	19.66	12.02				
b.		63	81		19.33	10.87	8.45	953	930	+1
					19.25	10.81				
9. (11/17/49)	14	90	65	21.63	17.57	10.15	7.45	871	860	+1
					17.58	10.09				
10. (12/2/49)	13.5	90	89	17.56	15.60	6.38	9.19	970	975	0
					15.56	6.40				
Average.....			75				7.78	1007	994	±5

* Experiments 1, 2, 3, closed chest-caval technic, 5 per cent added to rotameter values for coronary flow according to the data of Eckenhoff and co-workers.[6] Adjusted figures are in parentheses. Experiments 4–10, open chest-pulmonary artery technic. Mean carotid blood pressure was recorded optically with the Gregg manometer.

RESULTS

The results of these experiments are presented in table 1. Examination of the data discloses that the Fick procedure was tested under a variety of conditions. Oxygen consumption varied from 21–94 cc. per minute; arteriovenous differences from 2.01 to 12.40 volumes per cent, flows from 668–1463 cc. per minute, and mean blood pressure from 63–160 mm. Hg. In the table, comparisons of the Fick procedure with ±8 per cent. The greatest deviation, and the only one of this magnitude (+17 per cent) observed in Experiment 5, probably reflects inordinately large technical errors resulting from a small oxygen consumption, and very low arteriovenous difference.

The cardiac output during these experiments was both constant and variable. During eleven of the test periods, the flow and mean blood pressure remained essentially constant. Repre-

sentative rotameter curves from such experiments are shown in figure 2. Respiratory variations in flow, as seen in these records, occurred in all experiments. Although the magnitude of these variations differed, no influence on comparative results was noted. This might be expected, since these deviations about the mean are regular and relatively small. With constant flow, the rate of oxygen consumption was even and the resulting linearity of the oxygen slopes,

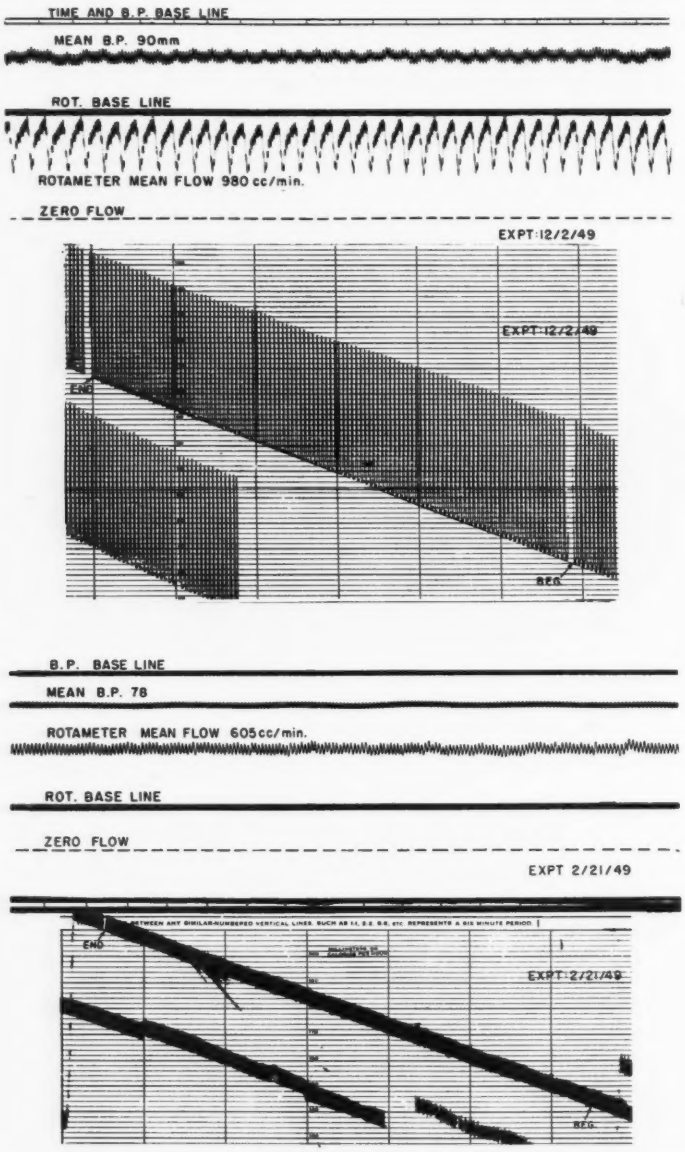

FIG. 2.—Flow and oxygen consumption curves from open (upper two) and closed-chest (lower two) dogs, with constant cardiac output and mean blood pressure. Time, 6 seconds.

as shown in figure 2, improved the accuracy with which oxygen uptake could be measured.

Sizeable irregularities in flow resulted from an uneven infusion rate in two experiments (table 1: 4a and 6b). Although the cardiac output varied ±30–40 per cent for at least one-half the test period, the agreement of the two methods in these instances does not appear to be affected. Figure 3 shows sections of records from these experiments.

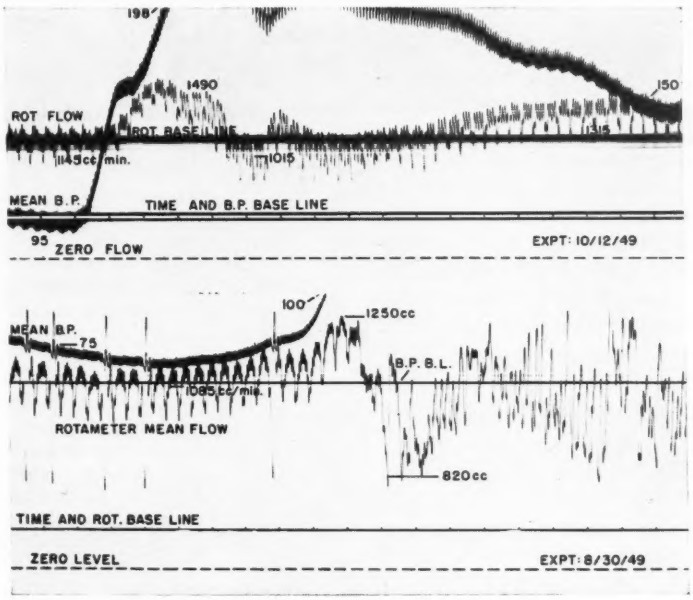

FIG. 3.—Flow curves from open-chest dogs with variable cardiac output and mean blood pressure. Time, 6 seconds.

DISCUSSION

Under the condition of these experiments, the Fick method accurately measured the average minute output of the heart. During the majority of the determinations, the output remained constant, but in two experiments with considerable variation in flow, good agreement was also noted. This is not surprising; for the Fick equation should remain valid with variable flow, if an average oxygen uptake and arteriovenous difference is obtainable with the technics used. Naturally, this demands continuous blood sampling over the entire period that oxygen uptake is being measured.

The small scatter of results which does persist in this work may be explained when known technical errors in the Fick and direct methods are considered.

The comparisons with the least technical error are those in which direct measurements of output were made in the pulmonary artery. In the Fick procedure, the error in measuring oxygen uptake, in the absence of leaks, is determined by the accuracy with which the oxygen slope can be read, and approximates 5 per cent. The error in determining the arteriovenous difference may be judged by noting the average difference of duplicate blood oxygen analyses which is 0.033 volumes per cent for the twenty-six pairs in table 1 (only one pair of samples differs more than 0.08 volumes per cent). A glance at the table shows that such differences cannot introduce an error of more than 1 or 2 per cent in the Fick method. The error introduced by the rotameter in these comparisons is also small. With the use of a pump system, we were able to show that this instrument measures flow within ±3 per cent, and this is not significantly altered by changes in viscosity or flow pattern over a wide range.

Therefore, when the estimated errors in the two methods are considered, the probable deviation which may occur on a technical basis approximates ±10 per cent.

In the three comparisons in which vena caval flow values served as the standard of reference, the error in the Fick procedure is the same as outlined above. The error in the rotameter method is increased somewhat, since a value for coronary flow can only be approximated. The results of these comparisons are within the same range as those using the more accurate pulmonary artery technic. The data from these experiments has been included in this report, since it supplies additional information on the accuracy of the Fick method in closed-chest dogs with spontaneous respiration.

Although this work was performed on operated animals, there is no reason to believe that the accuracy which has been demonstrated for the Fick method will be altered in the unanesthetized dog, provided that technical errors do not exceed those in the present work.

Summary

When the Fick procedure was compared with a direct method of high accuracy, excellent agreement was observed in a variety of hemodynamic states. Twelve of thirteen comparisons in the present work agreed within less than ±8 per cent. This was within the range of error which could exist on the basis of known technical inaccuracies.

Addendum

Since this manuscript was submitted, Huggins and others, Am. J. Physiol. **160:** 183, 1950, have compared cardiac input measured by the rotameter with output by the Fick procedure, the latter serving as the reference method. These comparisons, which range from +26 to −29 per cent, are not believed to serve as a measure of the accuracy of either method since (1) the rotameter did not measure coronary flow and thus underestimated total cardiac input; (2) the venous sample in the Fick procedure did not include coronary venous blood and thus caused an overestimation of total cardiac output; (3) the method of Roughton and Scholander for blood O_2 content is less accurate than the Van Slyke technic and its use therefore increased the probable error in the determination of the O_2 A-V difference. The vagaries noted by Huggins in the operation of the rotameter per se, do not occur if the line voltage is kept constant, the blood is properly filtered before calibration, and the calibration is made at the temperature and viscosity existing at the time of flow measurement. Under these conditions, rotameter calibration curves in our series are found to vary no more than 3 per cent from day to day.

Acknowledgments

Acknowledgment is made of the technical assistance of Mr. L. J. Czerwonka and Private E. M. Khouri.

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The Response of the Flicker Fusion Threshold to Nitroglycerin and Its Potential Value in the Diagnosis, Prognosis, and Therapy of Subclinical and Clinical Cardiovascular Disease

By L. R. Krasno, Ph.D., M.D., and A. C. Ivy, Ph.D., M.D.

Flicker fusion threshold (F.F.T.) means the frequency with which successive flashes of light must occur to just appear to the eye free from flicker. A simple portable machine is described which will deliver flashes of light at any required interval. Patients with hypertension or anemia have a lower than normal F.F.T.; furthermore, administration of nitroglycerin, 0.4 mg. sublingually, or papaverine, intravenously, raises the threshold in patients with hypertension and coronary disease and lowers it in normal individuals. It is suggested that this test may be of use in the diagnosis of equivocal cases and for the evaluation of therapeutic measures.

Introduction

THE purpose of this report is twofold. *First*, we shall describe a simply operated, accurate, and relatively sturdy machine, called a "flicker photometer," or "flicker meter," which may be used in a physician's office during routine physical examinations for the determination of the patient's visual threshold for the fusion frequency of flicker. *Second*, we shall indicate the potential usefulness of determining the response of the flicker fusion threshold (F.F.T.) to nitroglycerin in the diagnosis, prognosis, and therapy of subclinical cardiovascular disease. The response may in time prove to be practical for detecting a tendency toward coronary and hypertensive cardiovascular disease.

The Flicker Fusion Threshold (F.F.T.)

The threshold of the fusion frequency of flicker refers to that frequency of successive flashes of light at which the light stimulus appears to be continuous in intensity or free from flicker. For example, the ordinary Mazda electric lamp is usually supplied with a 60-cycle alternating current and the light stimulus from the lamp under these conditions does not flicker. However, if the 60 cycle alternating current is reduced to 50 cycles some persons will observe the lamp to flicker; and if reduced to 40 cycles, all "normal" persons will observe it to flicker.

The fusion frequency of flicker is among the most fundamental of visual phenomena.[1] The more intimate physiology of the phenomena has been studied in recent years by Crozier[2] and Selig Hecht.[3]

The apparatus required to study the more intimate physiology of flicker fusion phenomena is quite bulky and relatively expensive. In 1939 when we desired to ascertain if the F.F.T. might be used to measure objectively the subjective feeling of physical and mental tiredness in a patient, the machine we designed was heavy and bulky and required two persons to move it. In 1941, we constructed a small portable and inexpensive machine, which we used throughout the war in a study of the effect of hypoxia on bodily functions and the effect of certain drugs thereon.[4] This machine was not sturdy, and considerable skill was required in its operation. The present machine has been developed during the past three years. Our experience with its use convinces us that it is sturdy and reliable and that almost any adult can learn to operate it within ten minutes. Patients learn to follow instructions within three minutes or after 5 or 10 trials.

The Determination of the F.F.T.

The Flicker Photometer or Flicker Meter. A 6 volt tungsten lamp, which is connected with a 110 A.C.

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lighting circuit, serves as a constant source of light. The light is mechanically interrupted by placing the lamp within the lumen of a metal cylinder which contains one rectangular window so that when the cylinder is rotated by a motor under the control of a frequency oscillator, the light is on half of the time and the cut-off and cut-on of the light approximates a square wave (fig. 1). (This avoids a waxing and waning of intensity which occurs when a disk in-

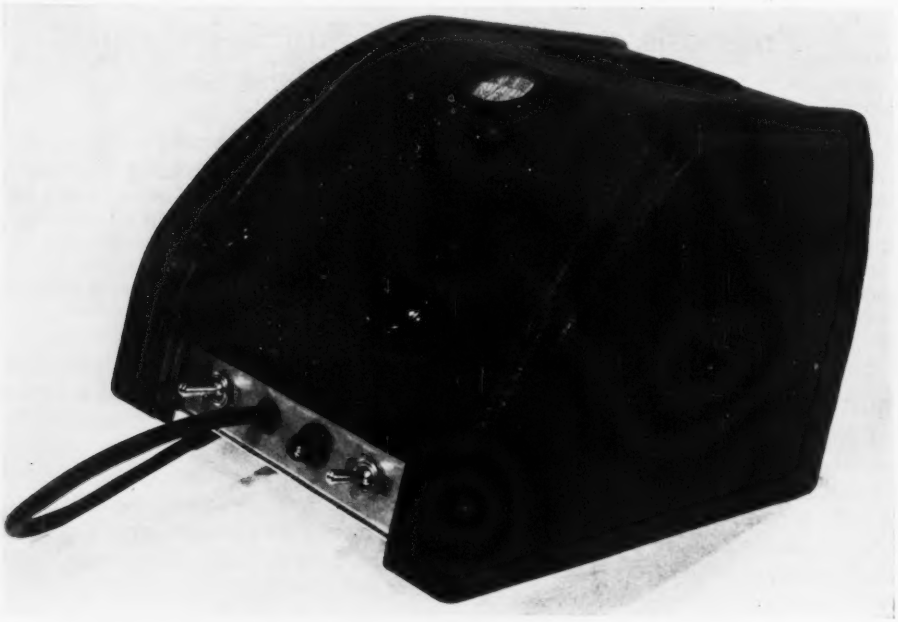

FIG. 1.—Operator's view of the flicker photometer (*above*).

FIG. 2.—Subject's view of the flicker photometer (*left*).

terrupter is used or when the light source is activated by a condenser discharge.) The light is directed to a frosted opal glass 1.3 by 1.6 cm. which the sub-

ject to be tested views. When the subject is seated at a distance of 1 meter, the image of the frosted glass falls within the fovea centralis of the retina. The intensity of the illumination measured on the subject's side of the frosted glass is 0.5 foot candle per square centimeter.

The machine has two dials. One of the dials controls the speed of the rotation of the cylinder and the frequency of the flashes of light; this is called the "control dial." The other dial is called the "memory dial," and is set after the control F.F.T. of the subject has been determined. The dials are calibrated in flashes per minutes.*

The Performance of the Test. The room in which the test is performed should be illuminated moderately or as it is ordinarily illuminated. Unless the source of illumination of the room is indirect, the subject's back should be turned to the source of light and the frosted glass must be free from glare. (A dark room provides ideal conditions, but is not necessary.) The illumination of the room, subject, and frosted glass should be the same from test to test.

The subject should be in a seated, resting position for at least 10 minutes before the test; smoking must be avoided for six hours prior to the test; alcohol must be avoided for at least twenty hours. Medication with hypnotics, vasodilator drugs, analeptics, and perhaps other drugs, should be considered in the interpretation of the results. If the patient normally wears glasses, the glasses should not be removed. We have always employed binocular vision, except for special experiments.

The subject is seated comfortably so that his eyes are 1.6 meters from the frosted glass to be illuminated later. A cord 1.6 meters in length is attached to the machine so that the distance may be maintained uniform from test to test. A chin rest is not necessary. The current supply of the machine is turned on.

The control dial, which controls the speed of the motor, is set at 3000 flashes per minute (50/sec.). The subject is then told that the frosted glass will be illuminated, that the light will be steady, and then it will flicker; and, when it flickers the subject should immediately say "now." When the subject says "now," the light is turned off to prevent fatigue. The rate is recorded on paper, the "memory dial" set, and the control dial turned 200 or 300 above the setting of the memory dial. The light is turned on, the dial is turned slowly down, until the subject says "now." The light is turned off.

Five such instructional trials are made. Then the operator records the readings and when 3 successive readings are approximately the same, that value is recorded as the F.F.T.

Results of the Test in Presumably Normal Subjects. We have determined the F.F.T. using many presumably normal subjects. The results on a random group of 32 such normal subjects are shown in table 1.

According to our observations it is rare for the F.F.T. of a normal subject to be less than 2400 flashes per minute or 40 per second. The same observation has been made by Enzer, Simonson, and Blankstein.[5] The average F.F.T. for their group was 44.9 flashes per second and for our group was 44.5 flashes per second.

It should be noted by inspecting table 1 that the range of flashes per second in 10 trials during one three-minute test period was greater than one flash per second in only 11 of the 32 subjects, and greater than 1.5 flashes per second in only 1 of the 32 subjects. This is the extent of the variation in the test found by others.[5] This variation is reduced considerably when the method indicated above is used because the greatest variation usually occurs in the first four or five trials when the subject is slow in calling the point at which flicker occurs.

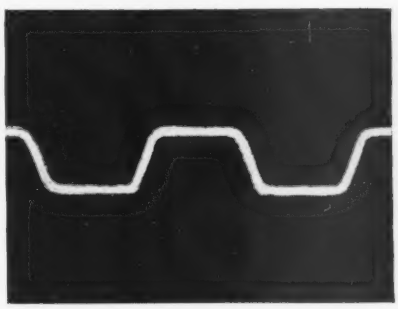

FIG. 3.—An oscillogram of the light intensity as viewed by the subject, showing that the cut-on and cut-off of the light is almost square.

FACTORS KNOWN TO AFFECT THE TEST

In our previous studies, the results of which have not been published, we observed that the F.F.T. was changed in some subjects by a feeling of fatigue,[6] by smoking, by climbing stairs, by a heavy meal, by sweating profusely, and by tension due to an oral examination.

We have found[4] that the degree of hypoxia associated with exposure in an altitude chamber to a simulated altitude of 18,000 ft. caused consistently an average decrease of 360 flashes per minute (6/sec.) in the F.F.T. The decrease first became evident at an altitude of 10,000 or 12,000 ft. which usually yields an arterial saturation of oxygen of approximately 85 per cent.

* This flicker photometer or flicker meter has been made for us by the Clinical Instruments Company of Chicago, Illinois.

Simonson, Enzer, and Blankstein[7] have found that the F.F.T. is related to age although in some young subjects the F.F.T. is as low as in older persons. Riddell[8] has reported that lowered visual acuity decreases or impairs the threshold, though Enzer and his colleagues have stated that this statement cannot be generalized.

As far as we have been able to ascertain, Enzer, Simonson and Blankstein[5] are the only investigators who have studied the F.F.T. in patients with cardiovascular disease. They studied 21 patients with heart disease and hypertension and one with pernicious anemia on the theory that anoxia of the visual pathway due to local or general circulatory insufficiency should decrease or impair the F.F.T. They found that with the exception of two fully compensated cases of mitral stenosis, all the patients had an F.F.T. of less than 2400 per minute.

TABLE 1.—*Showing Results of Measuring the F.F.T. Ten Times after Five Initial Trials in Presumably Normal Subjects*

Subject	Age	Range (Flashes/sec.)	Mean	Subject	Age	Range (Flashes/sec.)	Mean
	Yrs.				*Yrs.*		
L. K.	35	45.8–47.0	46.6	Ma. G.	25	48.0–49.5	48.7
La.	26	47.0–47.6	47.3	C. W.	38	46.0–46.8	46.4
Ben	36	46.0–47.5	46.7	Gr.	30	45.1–46.5	45.8
D. F.	27	43.8–44.5	44.1	Ch.	22	44.8–45.1	44.9
H. R.	29	45.1–46.5	45.8	Col.	42	46.3–46.5	46.4
B. L.	28	45.0–45.6	45.3	Ha.	30	43.3–44.0	43.6
Kim	26	42.5–44.0	43.1	Haw	26	43.0–44.5	43.7
Fl	25	42.5–44.5	43.1	Syl.	24	39.5–40.5	40.0
R. W.	20	45.0–45.5	45.3	Max	24	42.0–43.1	42.5
Mrs.	25	46.0–47.0	46.5	Ed.	23	45.5–46.5	46.0
Lit	28	45.5–47.3	44.4	P. O.	23	45.6–47.0	46.3
Sh	23	44.0–45.0	44.5	Ph.	21	44.5–44.5	44.5
Mo	37	40.5–41.0	40.7	Gr.	24	45.5–45.5	45.5
Dor	20	44.5–45.0	44.8	Le.	33	44.3–44.5	44.4
Gen	21	44.5–44.8	44.6	X	50	39.0–40.0	39.6
Kao	33	42.0–42.7	42.3	Nel	46	46.0–46.5	46.3

Average is 44.5 per second or 2670 per minute.

THE RESPONSE OF THE F.F.T. TO NITROGLYCERIN AS A TEST OF VASOSPASM OR VASOSPASTIC TENDENCY

Working Hypothesis.

As a working hypothesis, it was assumed, *first*, that since gross anatomic changes occur in the retinal blood vessels in hypertensive disease, the anatomic changes are probably preceded by a physiologic hypertonus or spasm of the arterioles. *Second*, it was assumed that if this were true, then nitroglycerin and other vasodilators should abolish the hypertonus or spasm of the arterioles of the retina and by an active hyperemia improve the oxygen supply of the retina which in turn would improve the F.F.T. It was assumed in the *third* place that if the arterioles of the retina and visual pathways were normal that nitroglycerin would dilate the arterioles, cause passive congestion of the retina and decrease or impair the F.F.T. In the *fourth* place it was assumed that in view of the intimacy of the embryologic development and vasomotor supply of the heart and retina, the detection of a vasospastic tendency in the retina might reflect a similar tendency in the coronary arterioles. Or, generalizing, we desired to ascertain whether the detection of the vasospastic tendency in the retinal vessels might be correlated with a vasospastic tendency or arterial vascular disease elsewhere in the body. This hypothesis regarding hypertension is supported by the vascular changes found by opthalmologic examination of the retina.

Vascular Changes in the Retina in Hypertension.

The opthalmologist recognizes three vascular abnormalities of the retinal arteries which may be related to hypertension: (1) the thickening of the arterial wall due to *aging*; (2) the thickening of the arterial wall plus localized nodular thickening due to *arteriosclerosis*; and (3), *contraction of the arteries* which may be localized to segments of the arteries or be generalized involving all the arteries of the retina.

Aging and arteriosclerosis of the retinal vessels, though sometimes seen in elderly persons, are more frequently seen in benign essential hypertension according to Elwyn.[9] Contraction of the retinal vessels, or arteriospastic retinitis, occurs in malignant hypertension, in a group of patients intermediate between the malignant and benign cases, in the hypertension of renal origin or of acute, subacute and chronic glomerulonephritis, and in the hypertension associated with preeclampsia and eclampsia of pregnancy. Furthermore, it is now well known that lumbodorsal sympathectomy is followed by a recession of the vascular changes in certain cases of essential hypertension.

Thus, on the basis of known facts, it is reasonable to expect the nitroglycerin-flicker test to detect the presence of retinal vasospasm in many patients with hypertension. However, the evidence suggesting that the detection of a vasospastic tendency in the retinal vessels may indicate a vasospastic tendency in the coronary vessels or elsewhere in the body in the absence of hypertension is not nearly so good.

Results

The Nitroglycerin-Flicker Test.—The F.F.T. of the patient is determined. Then, a tablet of nitroglycerin, 0.4 mg., is placed under the patient's tongue and the F.F.T. determined every two minutes for six minutes. This is referred to as the "*single test*". The "*double test*" consists of placing another tablet of nitroglycerin under the patient's tongue after the six-minute determination and then making a determination every two minutes for six more minutes. Intravenous papaverine may be used instead of nitroglycerin.

TABLE 2.—*Changes in F.F.T. Induced by Nitroglycerin (0.4 mg.) in 206 Patients without Evidence of Cardiovascular Disease, and Who Showed a "Normal" Response*

Age	No. of Patients	Nitroglycerin (Flashes/Min.)				Number Patients	
		Before		After (4-6 min.)		No Change	Decrease
		Avge.	Range	Avge.	Range		
10–19	24	2720	2500–3000	2540	2200–2900	0	24
20–29	40	2555	2400–2820	2375	2200–2700	0	40
30–39	37	2510	2300–2900	2325	2200–2710	0	37
40–49	44	2290	2000–2580	2215	2000–2500	0	44
50–59	29	2370	2015–2800	2300	2015–2700	0	29
60–69	20	2290	1980–2600	2160	1900–2400	0	20
70–79	8	2040	1860–2210	1910	1740–2100	0	8
80–89	3	2200	2040–2400	2160	2040–2340	0	3
Postural Hypotension.....	1	2340		2100		0	1

The expression "normal response" refers to the occurrence of an impairment or a decrease in the F.F.T. value after nitroglycerin. The expression "no change" indicates that the F.F.T. value or flashes per minute changed less than 60 per minute. The expression "abnormal response" indicates that the F.F.T. improved or an increase in the F.F.T. value occurred. In case "no change" occurs the "double test" is used.

Changes in F.F.T. Induced by Nitroglycerin in 110 Patients without Evidence of Cardiovascular Disease.—Table 2 provides a summary of the data obtained from 206 patients who did not have any clinical evidence of cardiovascular disease and who showed either "no change" or a "normal response."

Table 3 provides data on 62 patients without

clinical evidence of cardiovascular disease and who showed an "abnormal response" or evidence of vasospasm in the retinal vessels. In 32 of these patients the response became normal on general hygienic treatment plus papaverine; on withdrawal of the papaverine the response became abnormal again.

It should be noted that the response became normal in the patients with anemia when the hemoglobin returned to normal under treatment. The one patient with postural hypotension showed a "normal response," that is, the F.F.T. was impaired. The six diabetic patients showed an abnormal response. These were mild cases since the hyperglycemia and glycosuria were controlled by diet alone. Six patients with pre-eclamptic symptoms showed an "abnormal" response which became "normal" after delivery.

TABLE 3.—*Changes in F.F.T. Induced by Nitroglycerin (0.4 mg.) in 62 Patients without Clinical Evidence of Cardiovascular Disease and Who Showed an "Abnormal" Response*

Clinical Condition	No. Patients	Age	Nitroglycerin				Response After Treatment
			Before		After (4–6 mins.)		
			Avge	Range (Flashes/Min.)	Avge.	Range (Flashes/Min.)	
Routine examination	32	37–54	2319	2060–2520	2500	2300–2670	On treatment with papaverine, response normal; taken off papaverine, response abnormal
Pernicious anemia	2	39–42	2340	2280–2400	2460	2400–2520	Returned to normal
Secondary anemia	16	17–83	2250	1620–2700	2380	1800–2830	Normal response with normal Hb
Diabetic	6	43–62	2400	2100–2600	2520	2220–2700	Still abnormal in absence of glycosuria on dietary control
Pre-eclampsia	6	22–28	2200	1900–2400	2300	2000–2490	Normal after delivery

Changes in F.F.T. Induced by Nitroglycerin in Various Clinical Cardiovascular Conditions.—Two hundred and sixteen patients with various cardiovascular conditions have been studied with the nitroglycerin-flicker test; 139 had hypertension and 77 did not.

The results are shown in table 4. It should be noted that the test was abnormal in every patient. Two cases diagnosed as having coronary insufficiency without hypertension may be in error, but will be followed with interest to determine if the diagnosis is right.

One case history will be cited which is typical of 5 patients seen in this group showing that the results of the nitroglycerin-flicker test may be informative in patients with equivocal signs and symptoms of coronary disease.

Patient #16, a 42 year old man, stated that by May, 1948, he had experienced several attacks of mild, vague pressure and pain in the left chest which had radiated to the back of his head and down his left arm. The attacks had caused him enough concern to have consulted a physican who informed and assured him that the electrocardiogram, and heart and blood pressure were normal. Nevertheless, the attacks became more frequent first on effort and then at rest. Three other physicians whom he had consulted up to March, 1949, assured him that his electrocardiogram and heart were normal. At that time we found his electrocardiogram and blood pressure to be within normal limits, but his nitroglycerin F.F.T. test was "abnormal" or revealed a vasospastic tendency. He was advised to alter the nature of his work and living and placed on papaverine when it was found that this drug, when administered in 6 grain doses daily, gave a normal nitroglycerin-F.F.T. test and relieved the patient's symptoms. The patient did not follow our advice longer than a month, because during April and May he had had three electrocardiograms made by other physicians who had declared them to be normal. In June the patient returned to us and was admitted to the Hospital with a typical picture of an occlusion of the anterior coronary artery.

In the course of this work it has been found repeatedly that aminophylline, phenobarbital, and veratrum veride (Vertavis) did not alter the abnormal response to the nitroglycerin-F.F.T. test. On the contrary, papaverine intravenously may be substituted for nitroglycerin in the test. Furthermore, one grain of papaverine 3 or 4 times a day converted the "ab-

normal" to a "normal" response in 60 patients. Withdrawal of papaverine resulted in an "abnormal" response within 3 or 4 days. The effect of papaverine in the other patients was not determined, because the patients were not under our care.

Aminophylline intravenously has not yielded as clear cut dilation of the retinal vessels as papaverine intravenously or nitroglycerin under the tongue. This may be a factor of dosage, and further study than we have made would be required to warrant a conclusion.

Changes in F.F.T. Induced by Nitroglycerin in Patients with Cardiovascular Lesions Other than Hypertension and Coronary Heart Disease.—So far we have studied only 20 patients in this catagory. The results are shown in table 5. In none of these patients was the heart decompensated.

It is worthy of note that the patient diagnosed as having a "cardiac neurosis" had a normal electrocardiogram and F.F.T. The patients with thromboangiitis obliterans (Buerger's disease) gave an abnormal response.

The Effect of a Second Dose of Nitroglycerin (The Double Test) on the F.F.T. in Patients with Hypertension and Coronary Heart Disease.—Illustrative results on 7 patients with slightly elevated blood pressure or with known coronary heart disease are shown in table 6. In these patients it is to be noted that the second dose of nitroglycerin produced a "normal" response. However, in three patients with a very high blood pressure due to essential hypertension, the first dose of nitroglycerin may cause no change or only a slight increase or "abnormal" response and the second dose may cause a greater increase or "abnormal" response (table 6). This would indicate that the vasospastic tendency is more "fixed" in some patients than in others.

Possible Value of the Test in the Management of Diseases Due to or Complicated with Vasospasm.—We have been maintaining a number of patients on papaverine. By using either nitroglycerin sublingually or papaverine (50 mg.) intravenously as the dilator, we have been able to ascertain whether the patient

TABLE 4.—*Showing Change in F.F.T. with Nitroglycerin (0.4 mg.) in Various Clinical Cardiovascular Conditions (flashes/min.) in 216 Patients*

Clinical condition	No. Pts.	FCG abnor.	Nitroglycerin				No change	Increase
			Before		After			
			Avge.	Range	Avge.	Range		
Hypertension *without** history of cor. H.D. age 17–87 yrs.	78	47	2200	1620–2580	2330	1740–2750	0	78*
Hypertension *with* history of cor. H.D. (infar.) age 56–72 yrs.	33	27†	2140	1980–2400	2300	2130–2550	0	33
Hypertension with angina pectoris age 56–70 yrs.	14	7	2080	1980–2200	2250	2040–2400	0	14
Hypertension, malignant	14	12	1620	1300–1840	1800	1600–2040	0	14
Without hypertension, myocard. infar. age 42–72 yrs.	16	12††	2075	1860–2280	2215	2010–2450	0	16
Without hypertension, angina pectoris age 36–52 yrs.	19	4	2240	2040–2400	2410	2160–2670	0	19
Without hypertension, coronary insufficiency age 36–70 yrs.	33	11§	2220	2000–2550	2350	2200–2600	0	33
Without hypertension, generalized arteriosclerosis	9	2	2220	2100–2400	2390	2220–2580	0	9

* This group should be divided theoretically into those with and without generalized arteriosclerosis.

** All but one gave an "abnormal response"; that patient gave a normal response because he was on full doses of papaverine.

† ECG not made recently on 3 patients.

†† ECG not made recently on 1 patient.

§ ECG not made recently on 6 patients.

was receiving sufficient papaverine to obtain complete abolition of the vasospasm.

Although we have had no patients of our own on potassium thiocyanate, the test, using either nitroglycerin or papaverine intravenously, may be useful in ascertaining whether the patient is obtaining a therapeutically adequate dose of thiocyanate.

TABLE 5.—*Patients with Non-Hypertensive and Non-Coronary Cardiac Lesions**

Patient	Age	Nitroglycerin F.F.T.				Ecg.	Clinical Diagnosis
		Before	After				
			2 min.	4 min.	6 min.		
1	32	2340	2100	2100	2000	Positive	Sinus tachycardia
2	43	2500	2200	2100	2100	Positive	Extrasystoles
3†	41	2300	2400	2550	2550	Normal	Buerger's disease
4	70	2400	2300	2100	2100	Positive	Bundle branch block
5	44	2340	2340	2340	2340	Positive	Myocardial insuff.
6	63	2220	2200	2160	2100	Positive	Auricular fibrill.
7	66	2340	2340	2340	2340	Normal limits	Cardiac neurosis
8	65	2520	2460	2400	2340	Positive	Auricular fibrill.
9	43	2340	2340	2340	2340	Positive	Auricular fibrill.
10	30	2460	2400	2340	2340	Normal limits	Congenital patent ductus art.
11	28	2340	2160	2160	2160	Positive	Old rheumatic heart

* Nine additional patients with cardiac arrhythmias responded similarly.
† We now have 21 cases which act similarly.

TABLE 6.—*The Effect of a Second Dose of Nitroglycerin on the F.F.T. in Patients with Hypertension and Coronary Heart Disease. (F.F.T. = flashes/min.)**

Patient	F.F.T. before nitro.	F.F.T. after nitro.				F.F.T. before second dose of nitro.	F.F.T. after 2nd dose of nitro.			
		2 min.	4 min.	6 min.	Change		2 min.	4 min.	6 min.	Change
1	2130	2250	2250	2250	+120	2250	2160	2100	2040	−210
2	2040	2100	2160	2160	+120	2160	2040	2100	2040	−120
3	1920	1950	1980	2070	+150	2070	1920	1920	1920	−150
4	2100	2300	2300	2400	+300	2400	2340	2280	2220	−180
5	2200	2300	2400	2400	+200	2400	2350	2300	1950	−450
6	2800	2500	2500	2500	+100	2500	2400	2350	2300	−200
7	2400	2460	2520	2580	+180	2580	2400	2400	2340	−240
Patients with a "Relatively Fixed Hypertension"										
1	1300	1300	1300	1300		1300	1400	1500	1500	
2	1420	1420	1420	1420		1420	1500	1700	1700	
3	1800	1800	1800	1800		1800	1900	2220	2220	

* Thirty-three patients with hypertensive and coronary heart disease and 21 patients with malignant hypertension responded similarly.

DISCUSSION

As is true of all instruments used for measuring physiologic mechanisms or structures, the results obtained must be cautiously interpreted. This is particularly true of the nitroglycerin-flicker test we have proposed in this paper.

We believe that our results clearly show that the nitroglycerin-flicker test has revealed the presence of arterial hypertonus or spasm of the retinal arteries in 99 per cent of patients with existing hypertension or coronary arterial disease. We have also seen two patients with a normal resting electrocardiogram and blood pressure but with an "abnormal" nitroglycer-

in-flicker test who a few months later developed a clinically obvious coronary occlusion. This would suggest that this test may prove to be a valuable diagnostic aid where the evidence for the presence of angina pectoris and coronary occlusion is equivocal.

Our observations strongly support the view that the test may be very useful in ascertaining whether an alleged vasodilator drug is actually counteracting a vasospastic condition in a patient. This is certainly true of papaverine in the patients studied by us to date. This view of course is based on the assumption that the alleged vasodilator does not have a greater effect on the retinal vessels than on vessels elsewhere in the body. Whether the test will detect those persons who later will develop frank clinical evidence of hypertension or coronary arterial disease remains to be established. Nevertheless, it would seem obvious that any potential means for discovering a subclinical vasospastic tendency should receive extensive trial and study, since it appears certain that such a state precedes the clinical state and since potential patients should be warned against smoking and other activities which are believed to be conducive to the development of vascular disease associated with arterial hypertonus or spasm. It would also appear logical to resolve the vasospastic tendency at an early stage by the use of innocuous vasodilator drugs.

The nitroglycerin-flicker test should be studied in relation to the response to the cold pressor test, since Hines and Brown[11] found hypertension present five times more frequently in hyper- than in nonhyperreactors. The test should also be studied in relation to the Master two-step exercise test, since Master, Dack, Field and Horn[12] have reported that from 25 to 40 per cent of patients with coronary disease show nothing abnormal on physical examination and in the resting electrocardiogram. We have observed that when the blood pressure of a hypertensive patient decreases under management and a vasodilator drug such as papaverine, the flicker fusion threshold improves, which is an observation also made by Enzer, Simonson and Blankstein.[5] This might suggest that the immediate improvement with nitroglycerin might be due to a reduction of blood pressure rather than to the reduction of a vasomotor hypertonus or spasm. However, this suggestion is not tenable because the F.F.T. may improve after nitroglycerin in some patients with a normal blood pressure.

Summary

1. A sturdy and reliable flicker photometer or flicker meter which may be used in office practice has been designed. A method for using the apparatus for the determination of the threshold of the fusion frequency of flicker (F.F.T.) has been described.

2. The F.F.T. is lower than normal or impaired in patients with a definite hypertension or anemia and improves when these conditions respond to therapeutic control.

3. A *nitroglycerin-flicker test* has been devised. The test involves the determination of the F.F.T. before and at 2 minute intervals after placing nitroglycerin (0.4 mg.) under the tongue. In "normal" subjects nitroglycerin impaired the F.F.T. In 99 per cent of 216 patients with hypertension or coronary arterial disease, nitroglycerin improved the F.F.T.

4. In view of the fact that it is known that arteriospastic retinitis occurs in advanced cases of hypertension and that anoxia of the visual mechanism impairs the F.F.T., the improvement of the F.F.T. after nitroglycerin is interpreted as being due to the relief of vasospasm and a consequent active hyperemia. The impairment in the normal subject after nitroglycerin is interpreted as being due to vasodilation and a consequent passive hyperemia of the visual mechanism.

5. Some evidence is presented which suggests that the nitroglycerin-flicker test may prove to be a valuable diagnostic aid (a) for the presence of angina pectoris and coronary occlusion where the evidence is equivocal, (b) for the detection and management of persons who may later develop hypertension and coronary arterial disease, and (c) for ascertaining whether a certain dose of a vasodilator drug is actually entirely counteracting a vasospastic condition in a patient. These are potentialities which we believe merit much study.

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Evaluation of the Severity of Organic Occlusive Disease and Comparison of the Effectiveness of Various Procedures in Relaxing Peripheral Vasospasm.

Severity Evaluated by Determining Cutaneous Blood Flow in the Extremities from Records of Cutaneous Temperature during Maximum Vasodilation, Effectiveness of Spinal Anesthesia, Intravenous Tetraethyl Ammonium Ion (Etamon), Intravenous Benzylimidazoline (Priscoline) and Application of Heat to the Torso

By HAROLD D. GREEN, M.D., WILLIAM PERKINS, M.D. AND JOSEPH ABERNETHY, M.D.

Both organic occlusion and vasospasm are usually present in peripheral arterial vascular diseases. The degree of occlusion and the probable effectiveness of treatment designed to relax vasospasm can both be determined by measurement of the maximum increase in cutaneous blood flow produced by suitable vasodilator procedures. These studies included warming the torso and/or injections of tetraethylammonium chloride or benzylimidazoline, and administration of spinal anesthetic. The effects obtained with all three methods were closely comparable. Cutaneous blood flow was estimated from recordings of skin, room and body temperatures.

IN EVALUATING the status of the peripheral circulation in man, it is necessary to determine what maximum circulation is possible after all vasospasm has been abolished. By comparing the maximal flow in normal patients with that in patients with peripheral vascular disease after relaxation of all vasospasm, it is possible to determine quantitatively the amount of organic occlusion present in such conditions as thromboangitiis obliterans and arteriosclerosis.

In an earlier paper[1] it was demonstrated that tetraethyl ammonium, TEAC (Etamon*) and benzylimidazoline (Priscoline†) possess good potentialities for relaxing vasospasm. This paper is a further study and comparison of the effectiveness of larger doses of these drugs with that of application of heat to the torso (body warming), that of body warming plus the above drugs, and that of spinal anesthesia in a series of normal subjects and in patients with demonstrated occlusive peripheral vascular disease.

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* Tetraethyl ammonium chloride (Etamon). This drug was supplied by Parke, Davis and Co., Detroit, Mich.

† 2-benzyl-4, 5-imidazoline HCl (Priscoline). This drug was supplied by Ciba Pharmaceutical Products, Inc., Summit, N. J.

METHODS

Records of the cutaneous temperature were made with an 8-point Leeds and Northrup micromax using iron constantin thermocouples attached to the skin with a drop of collodion as was described in the previous report.[1] During the study, the subjects were placed in a room, the temperature of which was maintained at 19–20 C. The air was constantly circulated by a blower fan. The velocity of air circulation was approximately 25–50 feet per minute and the relative humidity was 50 per cent. The walls were cork insulated and had a surface temperature within ±1 degree of the air temperature. The cutaneous areas to be measured were exposed to the room air and care was taken to avoid all contact or close approximation of the mattress or blankets or other objects which might prevent rapid circulation of air past the exposed parts.

When, under the above conditions, the cutaneous temperature is stable thermal equilibrium may be assumed to be present between the rate of delivery of heat to the skin by the blood and the rate of loss of heat from the skin.[2] During equilibrium the rate of loss of heat to the environmental air may be represented by the equation:

$$C_a(T_s - T_a) = \textit{calories per minute} \qquad (1)$$

Where C_a equals the heat conductance of the air, i.e., the rate at which heat will be taken up by the air and walls per degree of temperature difference between the air and that of the surface of the skin and where T_s equals the surface temperature of the skin, and T_a equals the air temperature.

The rate of transfer of heat from the subcutaneous tissue to the outer surface of the skin may be computed as:

$$C_s(T_{vb} - T_s) = \textit{calories per minute} \qquad (2)$$

Where C_s is the heat conductance of the skin and T_{vb} is the subcutaneous temperature, assumed equal to the venous blood temperature, and T_s is the surface temperature of the skin.

The rate of delivery of heat to the subcutaneous tissues by the blood may be calculated as:

$$C_b(T_{ab} - T_{vb}) = \textit{calories per minute} \qquad (3)$$

Where C_b is the heat conductance of the blood, i.e., rate of delivery of heat by the blood per degree difference between arterial and venous blood temperatures; T_{ab} is the arterial blood temperature; and T_{vb} is the venous blood temperature.

Under conditions of equilibrium, the right hand component of each of these equations must be equal. Therefore, we may say that:

$$C_a(T_s - T_a) = C_s(T_{vb} - T_s) = C_b(T_{ab} - T_{vb}) \qquad (4)$$

Animal experiments[2] demonstrate that the heat conductance of the skin itself is quite rapid, i.e., under a variety of conditions the subcutaneous and surface temperatures proved to be practically identical. We may, therefore, by assuming T_{vb} to be approximately equal to T_s, simplify Equation (4) to:

$$C_a(T_s - T_a) = C_b(T_{ab} - T_s) \qquad (5)$$

and by rearranging we get:

$$\frac{C_b}{C_a} = \frac{T_s - T_a}{T_{ab} - T_s} \qquad (6)$$

The quantity C_b is equal to the flow of blood per minute through the skin (F_b) in cc. per minute times the heat capacity of blood (K_b) which is approximately one small calorie per cc. per degree centigrade change of temperature. C_a is a term which expresses the rate of heat loss by the skin, per degree difference of temperature between the skin and the air and walls. It may be considered to be composed of a constant (R) representing the net radiation loss plus a variable representing the conductive heat loss. The latter is equal to the flow of air (F_a) past the skin area in cc. per minute times the heat capacity of the air (K_a), also expressible in calories per degree per unit volume of air. Substituting these terms in Equation (6) gives:

$$\frac{F_b \cdot K_b}{F_a \cdot K_a + R} = \frac{T_s - T_a}{T_{ab} - T_s} \qquad (7)$$

K_a, K_b and R are constants and, under the conditions of our experiments, F_a may be taken to be constant so that Equation (7) may be reduced to

$$F_b \cdot K = \frac{T_s - T_a}{T_{ab} - T_s} = r \qquad (8)$$

Where

$$K = \frac{K_b}{F_a \cdot K_a + R}$$

$F_b \cdot K$ is the ratio of the difference between skin and air temperatures to the difference between arterial blood and skin temperatures. If we could evaluate K we could compute the blood flow per unit area of skin. This is not at the moment practical. However, since K may be expected to remain relatively constant in a given experimental set up, we can use the expression $F_b \cdot K$ as a measure of the *relative blood flow* from time to time in the same subject; and if experimental conditions remain constant, from subject to subject. This expression is called the *thermal circulation index* (r) by Burton[3] and we shall use this expression in this paper for the relative blood flow. Burton has prepared a nomogram for the rapid calculation of this index from the data on air, skin and arterial blood temperatures.[4]

The relationship between cutaneous temperature and blood flow, as represented by the thermal circulation index, may be illustrated by computing the index for a few skin temperatures. Using 37 C. for arterial blood temperature and 20 C. for room temperature, we would obtain the following:

Cutaneous Temperature	Thermal Circulation Index	Increment in Index	Percentile Increase in index
degrees C.			
21	0.06	0.15	250
22	0.21		
28	0.89	0.23	26
29	1.12		
35	7.5	9.5	125
36	16.0		

Thus we see that at low skin temperatures a 1 degree rise represents a relatively small increase in flow, at medium temperatures 1 degree rise means a considerable increase in flow and at high temperatures 1 degree rise indicates a very marked increase in flow. Burton obtained similar changes in his computations, but because he expressed his results percentally, the important phenomena of the absolute increase of flow was masked.[3] (See above column of percentile increase.)

The normal subjects for this series of experiments were 16 medical students. Ten of the students served

as subjects for body warming, for Priscoline and for body warming plus Priscoline, and 10 served as subjects for body warming, for TEAC, and for body warming plus TEAC. Four of the subjects served for both groups of drugs studied. Two of the 3 subjects for spinal anesthetic also served as subjects for TEAC and one served for Priscoline. One or more of the types of study reported in this paper has been carried out on 85 patients. Three of these patients who received all the types of tests for comparative purposes are reported in this paper.

During the tests on the normal subjects, temperatures were recorded from the forehead, left little finger, left thigh, left shin, dorsum of the left foot and dorsum of the large and small toes. Blood pressure, measured with the sphygmomanometer cuff, and pulse rate were recorded prior to the administration of TEAC, Priscoline, or spinal anesthesia, and every four to five minutes for thirty to sixty minutes afterwards. Oral temperatures were taken at the beginning of each test and any subject with fever was omitted.

In each study, on the normal subjects, a control period of one hour elapsed during which strong cutaneous vasoconstriction was induced by exposing the subject to the cool environment. Men were exposed only in shorts; women were clad in a slip. In order to obtain satisfactory vasoconstriction it was found necessary to have the subjects refrain from eating within two hours and not to exercise within one hour before the test. The degree of exposure was not sufficient to induce spontaneous shivering. When the subject had become sufficiently chilled so that strong vasoconstriction was present as indicated by the decline in the temperatures of the fingers and toes approximately to room temperature, one of five procedures was carried out:

1. TEAC was injected intravenously over a thirty-minute period in the amount of up to 20 mg./Kg. dissolved in 250 ml. of normal saline. Total amounts given varied from 900 to 1300 mg. in the normal subjects.

2. In 6 subjects, Priscoline was injected intravenously in amounts up to 2 mg./Kg. over a thirty-minute period dissolved in 250 ml. of normal saline. The total intravenous doses were 110 to 135 mg. In 4 subjects the Priscoline was given in four divided doses of 50 mg. each intramuscularly at ten-minute intervals. The Priscoline was preceded with one to two tablets of Trasentine with phenobarbital.

3. Body warming was induced by covering the torso and any portions of the extremities that were not being used for temperature studies with two woolen blankets and by applying electric heating pads to the back and front of the chest.

4. For the study of the effect of body warming plus TEAC or plus Priscoline, the period of heating was followed by an injection of the appropriate drug in the amount and at the rate indicated above for the drug alone while continuing the body warming.

5. Spinal anesthesia was induced by 75 to 100 mg. of procaine injected so as to produce complete anesthesia to T 11 or higher.

The registration of cutaneous temperatures, blood pressure, pulse, etc., were continued either until maximum skin temperature had been reached or until at least an hour had elapsed in those patients in whom no evidence of vasodilatation was noted. On any one study, only one drug was injected. The study was then discontinued and if a further study was made on this subject, it was carried out on a subsequent day after another control period of one hour of cooling to allow for maximal vasoconstriction.

Results

Effects of the Cool Environment. The results of exposure to the cool environment in the various groups are summarized in columns (A) and (C) in table 1 and columns (A) and (D) in table 2, and in the first portions of all the figures. It should be noted that the lowest cutaneous temperatures reached and the most rapid rates of decline during the period of cooling were in the finger and the first and fifth toes; the next lowest were in the dorsum of the foot, the next in the shin, then in the thigh and finally in the forehead. The minimal thermal circulation indices for the first toe in the various experiments are summarized in table 4, column (A).

The Effects of TEAC Alone. The temperatures recorded in the first pair of columns of table 1; column (A) are those at the time TEAC was given and the readings found at the time of the maximum effect after TEAC was given are tabulated in the second pair of columns (B). Following the injection of TEAC, mild to moderate shivering was noted in all subjects. The time lag before the cutaneous temperatures began rising was less the faster the TEAC was given. The maximal thermal circulation indices corresponding to the large toe are summarized in table 4, column (B), where they may be compared with those of the subsequent experiments. The sequential changes in temperature in the finger and toes are illustrated in figure 1.

Priscoline Alone. The effects of Priscoline alone are summarized in column (D), table 1. No significant differences in the responses to 200 mg. of Priscoline given intramuscularly

and to 2 mg./Kg. of body weight given intravenously were noted and all results are pooled. Priscoline alone was significantly less efficient than TEAC alone in producing vasodilation in the toes, but produced almost as good average responses in the finger. Priscoline produced significantly better responses in the thigh than did TEAC, and tended to produce a rise in forehead temperature rather than a drop. It would seem that the former has a more selective vasodilating effect on the trunk while the latter has a more selective action on the extremities. As with the administration of TEAC alone, Priscoline produced mild to moderate shivering. The sequential changes in flow in the finger and first and fifth toes are illustrated in figure 2 and the maximal thermal circulation indices are summarized in table 4, column (B).

Effects of Body Warming. In 20 subjects, divided into two groups of 10 each, the torso was warmed, as described under "Methods,"

TABLE 1.—*Changes in Cutaneous Temperatures Produced by Intravenous TEAC and Priscoline in Normal Subjects*

	TEAC—10 subjects				Priscoline—10 subjects			
	A		B		C		D	
	Temperature at time TEAC given		Temperature at maximum effect after TEAC given		Temperature at time Priscoline given		Temperature at maximum effect after Priscoline given	
	Range	Average	Range	Average	Range	Average	Range	Average
Forehead	31.5–34.5	33.3	30.5–33.0	32.3	32.0–34.5	33.5	32.5–35.5	34.2
Finger	21.0–25.5	22.3	23.0–34.5	31.2	20.0–31.0	23.2	22.5–34.5	29.6
Thigh	28.5–33.5	30.5	29.5–34.5	31.6	29.0–33.0	30.6	29.5–35.0	33.0
Shin	27.5–30.0	29.0	28.0–32.0	30.0	27.5–31.5	29.1	28.0–33.0	29.7
Foot	25.0–28.5	26.9	30.0–34.0	32.4	24.0–28.5	26.7	24.0–31.0	28.7
1st toe	21.0–25.0	22.0	32.5–35.0	33.8	20.0–22.0	21.0	23.5–34.0	29.6
5th toe	21.0–25.0	22.1	31.5–34.5	33.7	19.5–22.0	21.0	21.5–34.5	28.2

TABLE 2.—*Effects of Warming Torso plus TEAC and Priscoline on Cutaneous Temperatures in Normal Subjects*

	TEAC—10 subjects*						Priscoline—10 subjects*					
	A		B		C		D		E		F	
	Temperature at the time heat applied to the torso		Maximum temperature after heat applied but before TEAC given		Maximum temperature after TEAC given		Temperature at the time heat applied to the torso		Maximum temperature after heat applied but before Priscoline given		Maximum temperature after Priscoline given	
	Range	Average	Range	Average	Range	Average	Range	Average	Range	Average	Range	Average
Forehead	32.5–35.0	33.0	33.0–35.0	33.8	32.0–35.0	32.8	32.0–35.0	33.4	34.0–36.0	34.2	34.0–36.5	35.0
Finger	18.0–30.0	21.7	29.5–36.5	34.0	32.0–36.0	34.6	19.0–30.0	22.0	26.5–36.0	33.4	31.0–36.0	34.4
Thigh	28.0–33.5	29.8	29.5–34.5	31.4	30.5–34.5	31.3	28.0–31.0	29.4	29.5–34.0	31.2	29.5–35.5	33.1
Shin	27.0–29.5	28.3	27.0–29.5	28.0	27.5–30.5	29.3	26.5–29.5	28.5	25.0–29.5	28.3	28.0–32.0	29.4
Foot	21.5–27.5	25.8	22.0–32.5	28.2	31.5–34.5	33.2	22.0–28.0	26.0	22.0–30.0	27.2	28.0–34.5	31.7
1st toe	19.0–24.0	21.0	21.5–34.0	27.7	33.0–35.0	34.0	20.0–22.0	20.8	20.0–32.5	25.9	32.5–36.0	33.5
5th toe	18.5–23.0	20.8	21.5–35.0	27.3	31.0–35.5	33.7	20.0–22.0	20.8	20.0–33.5	24.0	32.0–36.0	33.6

* These are the same subjects as those used for table 1, columns (A), (B), (C) and (D).

TABLE 3.—*Effect of Spinal Anesthesia on Three Normal Subjects*

	A		B	
	Temperature at time spinal anesthetic was given		Maximum temperature after spinal anesthetic was given	
	Range	Average	Range	Average
Forehead	32.0–33.0	32.7	31.5–33.0	32.2
Finger	20.0–21.2	20.5	20.0–31.2	27.4
Thigh	28.2–29.0	28.6	28.0–32.0	30.3
Shin	27.2–29.0	28.1	28.0–29.8	28.8
Dorsum of foot	22.6–26.4	24.3	29.5–32.5	30.8
1st toe	20.0–21.5	20.7	28.0–33.6	31.7
5th toe	20.0–21.5	20.7	29.6–34.0	32.0

TABLE 4.—*Summary of Thermal Circulation Indices for the Large Toe for All Experiments on Normal Subjects*

	A		B	
	Minimum indices before application of heat or drug		Maximum indices after application of heat or drug	
	Range	Average	Range	Average
TEAC alone	0.012–0.40	0.102	3.05 – 7.0	4.39
Priscoline alone	0.031–0.14	0.066	0.22 – 4.5	1.91
Heat to torso				
TEAC group	0.028–0.31	0.101	0.029– 4.0	1.68
Priscoline group	0.00 –0.11	0.050	0.012– 3.0	1.00
Application of drug while heat being applied to torso				
TEAC	—	—	3.12 – 7.5	4.82
Priscoline	—	—	2.6 –16.0	4.78
Spinal anesthesia	—	—	0.98 – 3.86	2.81

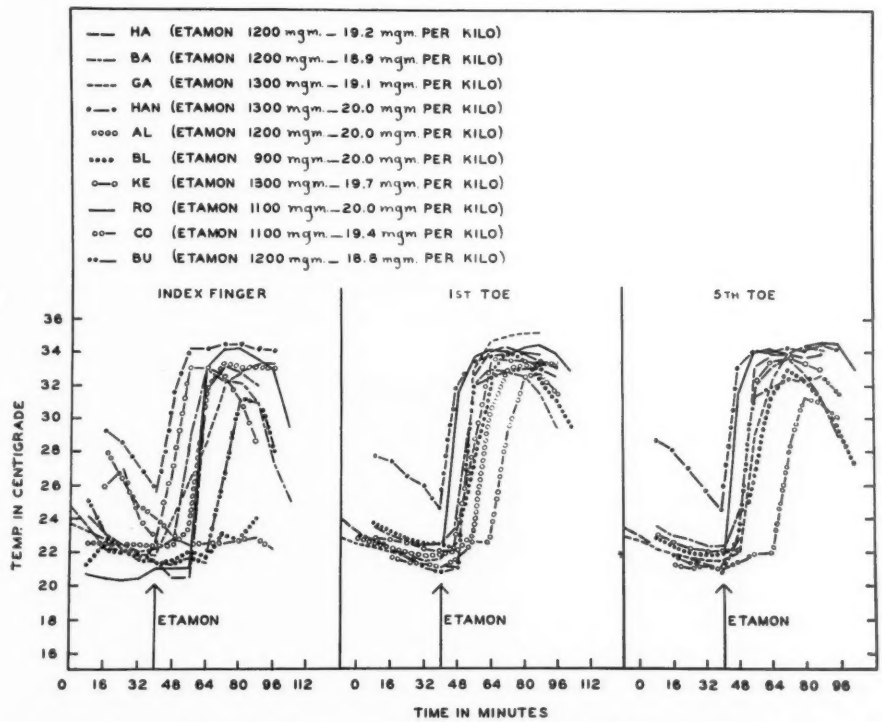

FIG. 1.—Sequential changes in temperature in the finger, first and fifth toes in response to intravenous injection of TEAC (Etamon) in 10 normal subjects. Abscissal scale: time in minutes; ordinate scale: cutaneous temperature in degrees centigrade. Zero time is beginning of period of cooling of body to induce vasoconstriction. Arrow indicates start of intravenous injection of TEAC. The total doses administered are indicated in the figure. Average room temperature during the tests on the various subjects ranged between 19.0 and 20.6 C. (average of averages 19.9 C.). The extremes reached for brief moments, due to opening the door to the constant temperature room were 17.2 and 21.5 C.

after maximal vasoconstriction had been obtained by the initial period of approximately one hour of cooling. The results are summarized in columns (B) and (E) in table 2. The rates of change of temperature in the finger and toes are illustrated in figures 3–6 and the maximal

thermal circulation indices in table 4, column (B).

Effects of TEAC after Warming the Torso. In 10 subjects, after the maximal possible vasodilation had been obtained in response to warming the torso, TEAC was given in the same dose and route of administration as that used above. The results on the various areas of the skin are summarized in table 2, column (C), the maximal thermal circulation indices are summarized in table 4, column (B), and the rates of change of temperatures are illustrated in figures 3 and 4. Approximately the same maximal temperatures were obtained in the toes but a significantly higher maximal temperature occurred in the fingers in response to body warming plus TEAC as compared with TEAC alone.

Effects of Priscoline after Warming the Torso. Table 2, Column (F), table 4, column (B), and figures 5 and 6 illustrate the responses to intravenous Priscoline while warming the torso. The responses to warming the torso in this group of subjects was essentially the same as that for the subjects used for table 2, column (B). The response to Priscoline during body warming,

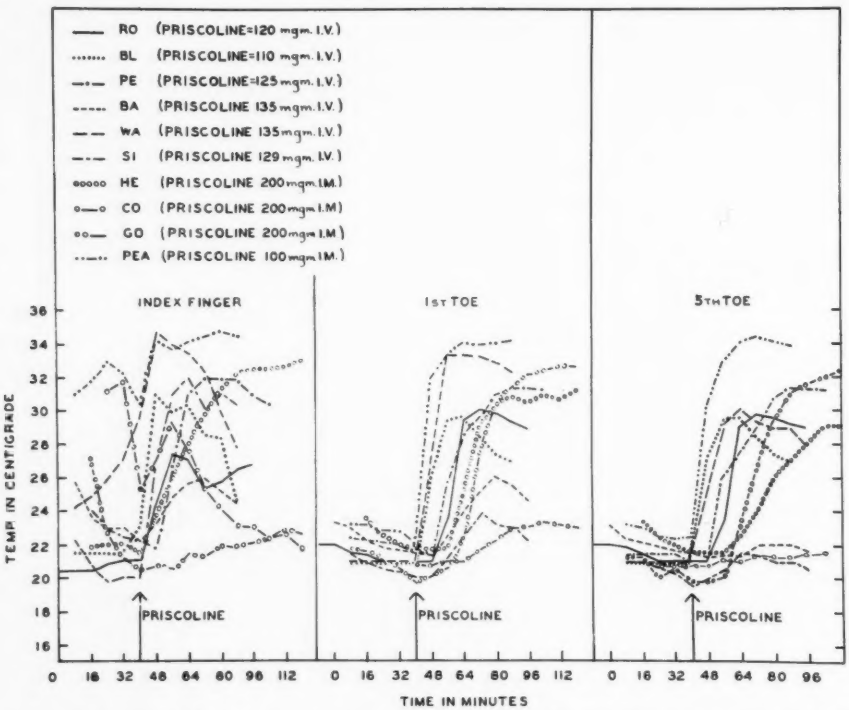

FIG. 2.—Sequential changes in cutaneous temperature in the finger and toes in response to Priscoline alone. See figure 1 legend for further details. The average room temperatures ranged from 19.5 to 20.8 C. (average of averages 20.2 C.); extremes 18.5 and 21.0 C.

FIGS. 3 AND 4.—Sequential changes in temperature in the middle finger, and first toe in 10 normal subjects in response to warming the torso with blankets plus two 150 watt electric pads, followed by the intravenous injection of TEAC. Warming of the torso was begun at point indicated by the first arrow and continued throughout the remainder of the test. Injection of TEAC was begun at point indicated by the second arrow. The apparent break in the curves was necessitated by the fact that various intervals elapsed between the beginning of body warming and the starting of the injection of TEAC. For further explanation, see figure 1 legend. Average room temperature during these tests ranged from 19.0 to 20.6 C. (average of averages 19.9 C.); momentary extremes 17.2 and 21.5 C.

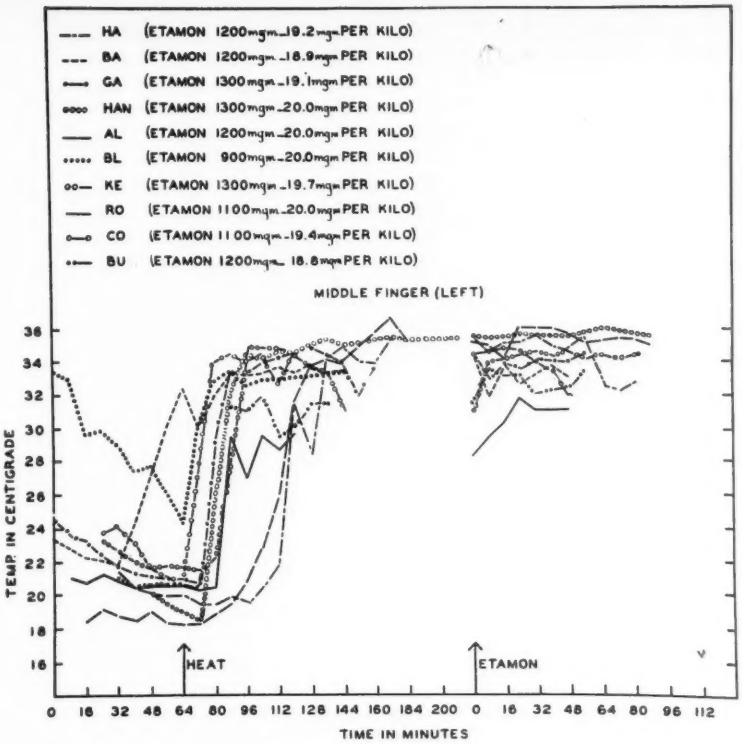
HA (ETAMON 1200mgm.-19.2mgm. PER KILO)
BA (ETAMON 1200mgm.-18.9mgm. PER KILO)
GA (ETAMON 1300mgm.-19.1mgm. PER KILO)
HAN (ETAMON 1300mgm.-20.0mgm. PER KILO)
AL (ETAMON 1200mgm.-20.0mgm. PER KILO)
BL (ETAMON 900mgm.-20.0mgm. PER KILO)
KE (ETAMON 1300mgm.-19.7mgm. PER KILO)
RO (ETAMON 1100mgm.-20.0mgm. PER KILO)
CO (ETAMON 1100mgm.-19.4mgm. PER KILO)
BU (ETAMON 1200mgm.-18.8mgm. PER KILO)
MIDDLE FINGER (LEFT)
TEMP. IN CENTIGRADE
HEAT
ETAMON
TIME IN MINUTES

FIG. 3

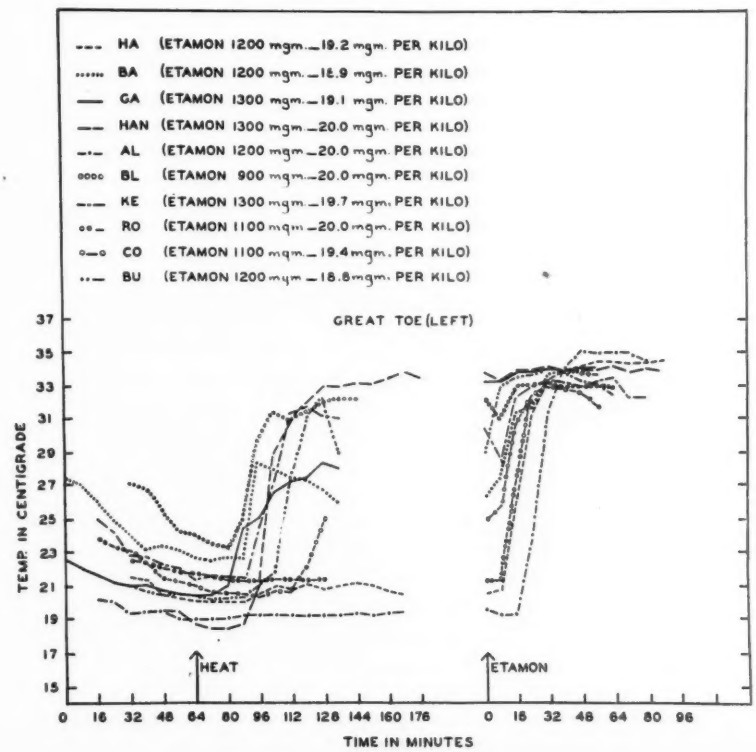
HA (ETAMON 1200 mgm.-19.2 mgm. PER KILO)
BA (ETAMON 1200 mgm.-18.9 mgm. PER KILO)
GA (ETAMON 1300 mgm.-19.1 mgm. PER KILO)
HAN (ETAMON 1300 mgm.-20.0 mgm. PER KILO)
AL (ETAMON 1200 mgm.-20.0 mgm. PER KILO)
BL (ETAMON 900 mgm.-20.0 mgm. PER KILO)
KE (ETAMON 1300 mgm.-19.7 mgm. PER KILO)
RO (ETAMON 1100 mgm.-20.0 mgm. PER KILO)
CO (ETAMON 1100 mgm.-19.4 mgm. PER KILO)
BU (ETAMON 1200 mgm.-18.8 mgm. PER KILO)
GREAT TOE (LEFT)
TEMP. IN CENTIGRADE
HEAT
ETAMON
TIME IN MINUTES

FIG. 4

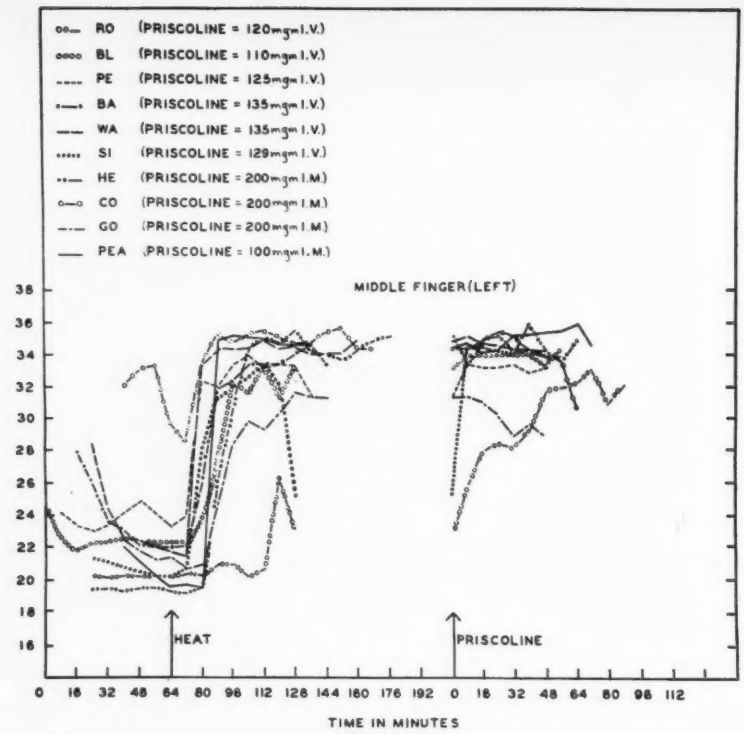

FIG. 5

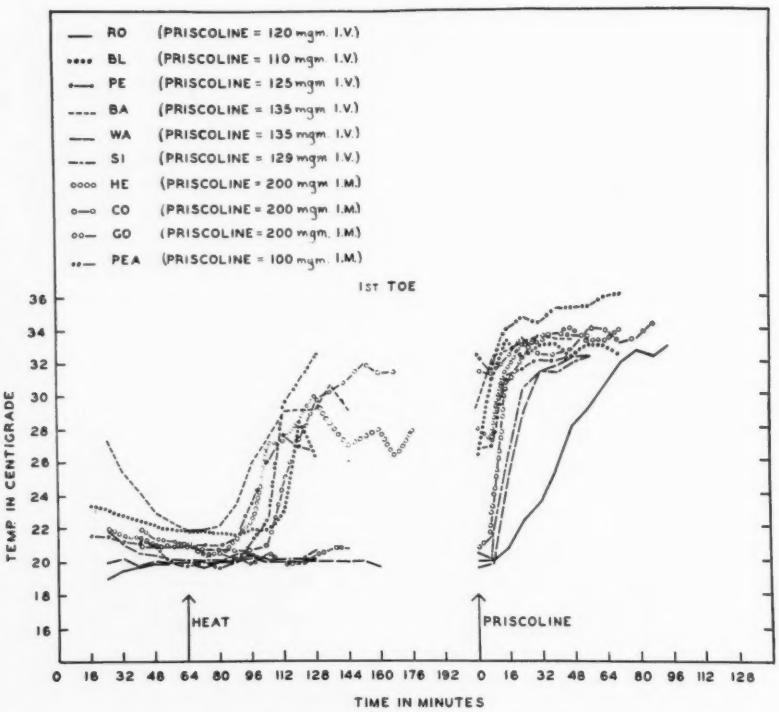

FIG. 6

FIG. 5 AND 6.—Sequential temperatures in the finger, and first toe in 10 normal subjects in response to warming of the torso followed by injection of Priscoline. For further explanation, see legend for figures 3 and 4. Average room temperature during these tests ranged from 19.5 to 20.0 C. (average of averages 19.9 C.), momentary changes 18.5 and 21.5 C.

however, was much more consistent and marked than it was with the subjects unwarmed.

Body warming plus Priscoline produced significantly higher temperatures in the finger, foot and toes than the use of Priscoline alone. The rate of rise of temperature was similar with body warming plus Priscoline, and body warming plus TEAC; the former produced a slightly higher thigh temperature, and the latter a slightly higher foot temperature. The thigh, shin and foot remained warmest during the period of development of vasoconstriction in response to cooling, but these portions did not warm to quite as high a temperature as the fingers and toes, after the application of heat to the torso plus either TEAC or Priscoline.

Miscellaneous Observations in Regard to TEAC and Priscoline in Normal Subjects. It was noted that the subjects ceased perspiring after receiving TEAC. In all subjects both systolic and diastolic blood pressures tended to rise slightly. The maximum systolic rise was 14 mm. Hg and the maximum diastolic rise was 30 mm. No relationship between blood pressure rise and rapidity of or degree of rise in cutaneous temperatures was noted. In 5 subjects the increase in diastolic pressure was 12 mm. or less. The blood pressure changes with the use of TEAC alone or with body warming were comparable. Pulse rates increased in all subjects 28 to 54 beats per minute.

It was noted that Priscoline did not cause perspiration to cease as did TEAC, and did not seem to increase perspiration. Following the injection of Priscoline, systolic pressures remained the same or rose slightly, the maximum rise being 18 mm. Diastolic pressures tended to fall, the maximum fall being 18 mm. In general, the less the rise in systolic pressure the greater the fall in diastolic pressure, and vice versa. In either case the pulse pressure increased. The pulse rates increased in 9 subjects 8 to 68 beats per minute; no change occurred in one. These changes were essentially the same in the heated and unheated subjects.

The Effects of Spinal Anesthesia in Normal Subjects. The results of spinal anesthesia on the various skin temperatures are summarized in table 3 and the sequential changes in temperature in the first toe in one of the subjects are reproduced in figure 7. The maximal thermal circulation indices are indicated in table 4, column (B). One subject received 100 mg. of procaine and 2 subjects 75 mg. One of the latter showed a 3 to 4 degree smaller response in the toes than with Priscoline or TEAC. All 3 subjects showed a slight fall in forehead temperature. One showed an increase in temperature of the finger to 31.5 C. In this subject the level of anesthesia was to and including T 5. The other 2 subjects showed no change in temperature of the finger with an anesthesia level to and including T 11. If the subject who showed a significantly lesser response to spinal anesthesia than to TEAC or Priscoline were omitted, the average final temperature levels in the toes and foot would be: first toe, 33.5; fifth toe, 33.3; foot 30.8 C. These values agree closely with those obtained by using heat plus TEAC or Priscoline or TEAC alone.

Comparison of Effects of TEAC, Priscoline and Spinal Anesthesia in Patients with Impaired Circulation. In patients with normal circulation in whom these agents produced rise in skin temperature approximating the maximum, large differences in blood flow would be necessary to produce significant differences in the recorded skin temperature in response to these agents. As a consequence, it is difficult to state precisely which of the three methods tested might be superior or whether they might be essentially equal in their capacity to relax vasospasm and thus unmask the degree of organic vascular occlusion in situations where there is only a very slight degree of organic occlusive disease. On the other hand, if the maximum possible circulation is small, relative to the normal, then small changes in blood flow will produce considerable alterations in the skin temperature, as indicated by the computations given under methods. Furthermore, it is precisely under these conditions that one wishes to know the relative effectiveness of various methods of relaxing vasospasm. We have, therefore, made comparisons of the three methods in 3 patients in whom there was demonstrated peripheral vascular disease. Plots of the sequential temperatures in these patients in response to TEAC, Priscoline and

spinal anesthesia are reproduced in figures 8, 9, and 10. Table 5 gives the maximal thermal circulation indices seen in these patients.

Figure 8 shows the temperature curves recorded on a 39 year old truck driver (K. D.) with a clinical diagnosis of Buerger's disease. He had a three year history of intermittent claudication and recently complained of pains in both feet at rest. The physical examination was negative except for absent dorsalis and posterior tibial pulses, and dependent rubor bilaterally. The normal value plotted is that of a typical normal subject. The results of the three different methods compare favorably with each other; all three indicate the presence of occlusive vascular disease. Spinal anesthesia was obtained through T 11.

Figure 9 shows the curves recorded during

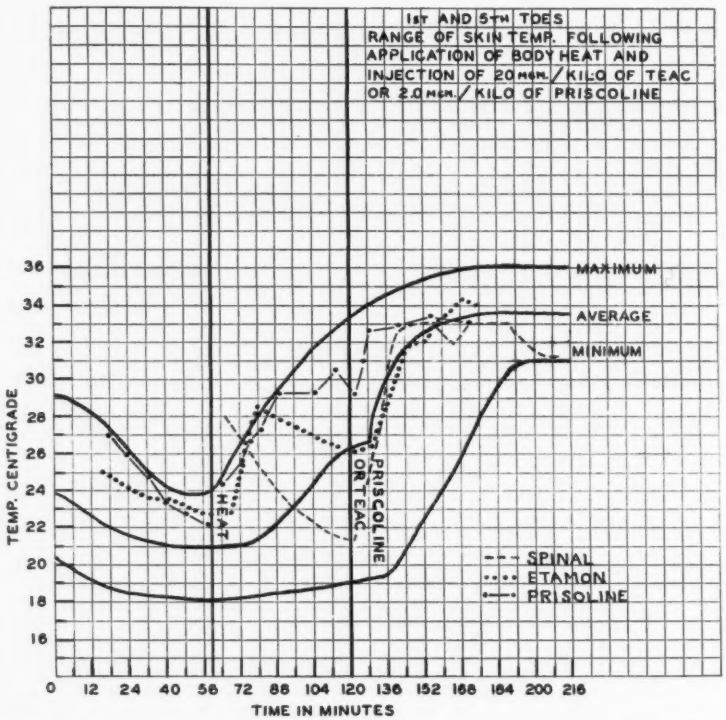

FIG. 7.—Temperature changes in first toe in a normal subject in response to 1200 mg. (18.9 mg./Kg.) of TEAC, 135 mg. Priscoline and to induction of spinal anesthesia up to and including T 5, using 100 mg. of procaine. These temperature responses are plotted on paper upon which are printed solid lines representing the extremes of temperatures found in the normal subjects reported in figures 1 to 6. This type of plot is being used for reporting the results of temperature studies to referring physicians. Room temperature for these studies varied from 19.3 to 21.2 C. (average 20.3 C.).

TABLE 5.—*Thermal Circulation Indices Corresponding to the Maximal Temperatures Reached in the Patients Illustrated in Figures 8, 9 and 10*

Test	KD (fig. 8)				WDM (fig. 9)				W (fig. 10)			
	Left foot		Right foot		Left foot		Right foot		Left foot		Right foot	
	1st toe	5th toe	1st toe	5th toe	1st toe	5th toe	1st toe	5th toe	1st toe	5th toe	1st toe	5th toe
Etamon plus body warming....	0.23	0.29	0.51	0.43	0.67	0.21	0.12	0.14	0.75	0.80	0.04	0.04
Priscoline plus body warming.	0.33	0.37	0.68	0.40	1.27	0.67	0.15	0.25	0.62	0.62	0.03	0.03
Spinal Anesthesia.....	0.58	0.45	0.55	0.17	1.35	1.07	0.15	0.31	1.66	1.28	0.05	0.04

studies on a 59 year old sheriff (W. D. M.) with a clinical diagnosis of arteriosclerotic occlusive disease in both feet. He complained of intermittent claudication of three months duration and of pains at rest in the right foot for three weeks. Physical examination revealed absent dorsalis pedis and posterior tibial pulses bilaterally. The right toes showed no temperature increase following any of the vasodilating procedures. The poorer response to TEAC plus heat in the left toes was believed to be a result of a drop in blood pressure from 170/85 to 100 60 during that procedure.

Figure 10 reproduces the temperature changes in response to the three methods of testing in J. A. W., a 58 year old man. For several years he had noted tiredness in his right foot and calf muscles when he walked two to three blocks. One month prior to the tests he had noted coldness, pallor and numbness of the entire right foot which lasted two hours. Examination revealed the distal half of the right foot to be cold and blue. The popliteal pulses were present bilaterally; the dorsalis pedis, and posterior tibial pulses were present, though weak in the left foot, but were absent in the right foot.

The thermal circulation indices for these 3 patients are summarized in table 5. The slightly higher temperatures and thermal circulation indices obtained in the left toes in these patients in response to spinal anesthesia, as compared with TEAC or Priscoline plus heat, is believed to be due principally to an artefact

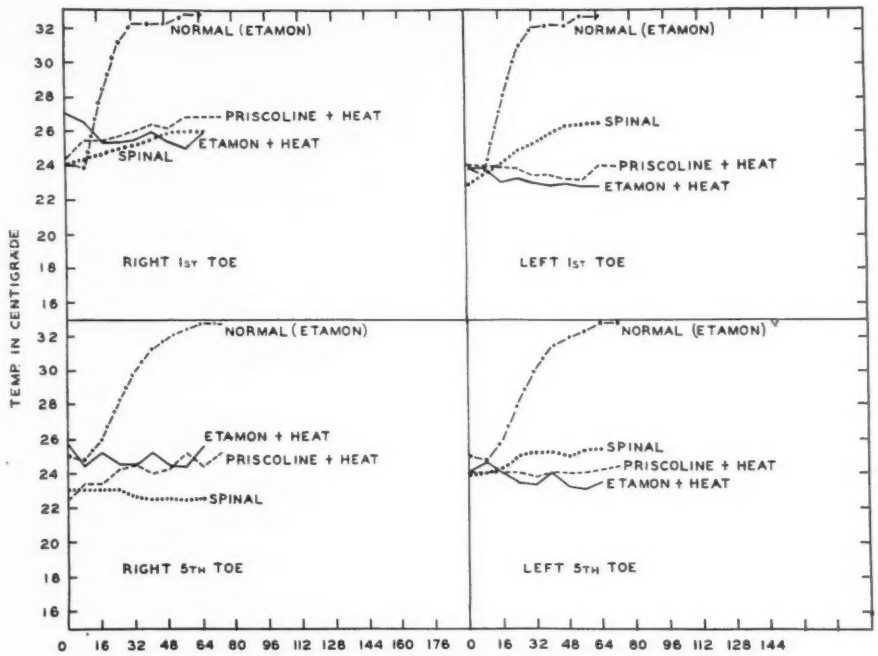

FIG. 8

FIGS. 8, 9 AND 10.—Superimposed temperature responses in 3 patients with demonstrated peripheral vascular disease in response to spinal anesthesia, to body warming plus TEAC and body warming plus Priscoline. See text for description of patients. Period of cooling to induce vasoconstriction, and period of warming torso omitted. Zero time-start of injection of drug. Heat plus Priscoline and heat plus TEAC indicate that these drugs were given after a period of one hour had elapsed during which the torso was warmed as indicated in the legend for figures 3 and 4. See text and legends for previous figures for further explanation.

FIG. 8 (Mr. K. D.)—1500 mg. TEAC; 150 mg. Priscoline; 75 mg. procaine, anesthesia through T 11; room temperature ranged from 20.0 to 22.0 C.(average 20.6 C.).

caused by the circumstance that for the spinal anesthesia the patients had to be placed in a different position in the room in which the air flow past the left foot was less than with the studies using TEAC or Priscoline.

Discussion

In view of the fact that approximately the same average maximal cutaneous temperature 34 C. (thermal index 4.7) was reached in the thermal equilibrium could be maintained with an average cutaneous temperature of 34 C., then under the conditions of our experiments the cutaneous blood flow would be

$$\frac{\frac{40\ Cal.}{M^2 \cdot hr.} \times 4}{(37° - 34°) \times \frac{60\ min.}{hr.} \times \frac{1\ Cal.}{L \cdot °C}}$$

$$= 0.87\ L/min./M^2 = 8.7\ ml./min./100\ cm.^2$$

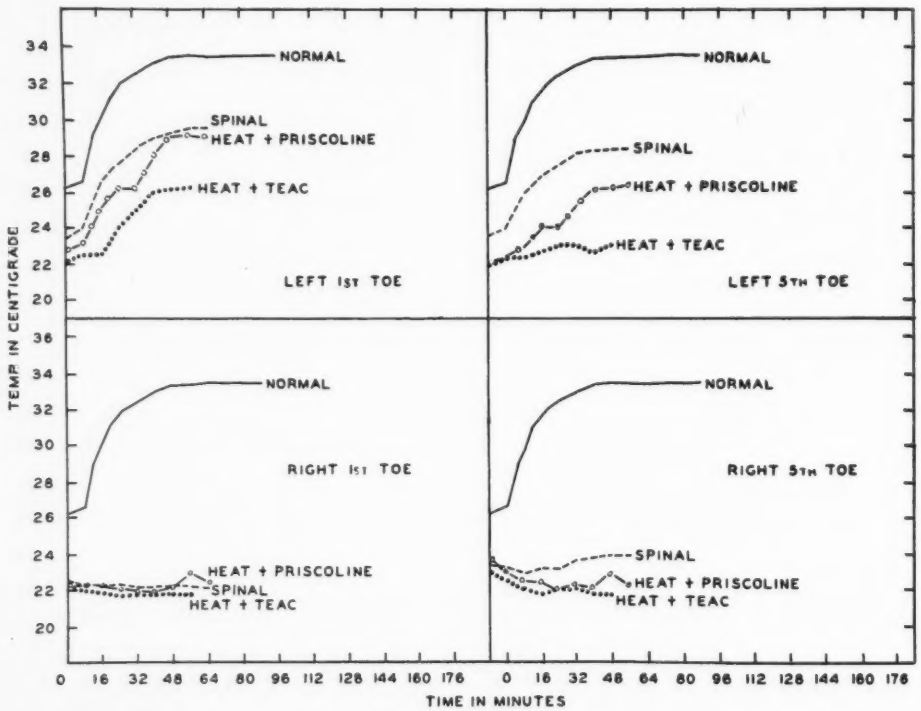

Fig. 9 (Mr. W. D. M.)—1680 mg. TEAC; 180 mg. Priscoline, 75 mg. procaine, anesthesia through T 7; extreme range of room temperature during the three tests was 19.3 to 20.8 C. (average 20.1 C.).

fingers, toes and forehead with body warming plus TEAC, or Priscoline, and for the toes with spinal anesthesia, it seems reasonable to assume that these values represent the average maximum possible rate of cutaneous circulation in normal subjects. Similarly, the average minimum temperature of 21 to 22 C. (thermal indices 0.06 to 0.21) may represent the normal maximal degree of vasoconstriction.

If we assume maximum metabolic activity of about four times basal, and assume that and if we assume the cardiac output to be elevated to four times basal this would mean that approximately 7 per cent of the cardiac output would be passing through the skin. Since, however, the distal portions show the higher temperature rise these areas may have higher rates of flow. As a first approximation we might, therefore, assume a thermal index of 4.7 (equal to a cutaneous temperature of 34 C.) to be equivalent to a blood flow of approximately 8.7 ml./min./100 cm^2.

Conversely, if we assume maintenance of thermal equilibrium at basal metabolism with an average cutaneous temperature of 21 C., the cutaneous blood flow would be

$$\frac{\frac{40\ Cal.}{M^2 \cdot hr.} \times 4}{(37° - 21°) \times \frac{60\ min.}{hr.} \times \frac{1\ Cal.}{L \cdot °C}}$$

$$= 0.036\ L/min./M^2 = 0.36\ ml./min./100\ cm.^2$$

equivalent to a thermal index of 0.06, and equal to approximately 1.2 per cent of the cardiac output (taken as 3.0 L/min./M²). Since, however, the torso and more proximal portions maintain temperatures much above 21 C., the actual circulation at maximal vasoconstriction in the distal parts of the extremities probably drops considerably below this figure. In view of the uncertainties involved, it is not possible to attempt any further approximation to the actual blood flow without direct measurement. Hoobler and associates[5] reported average maximum flows of 10.0 and minimum flows of 2.04 ml./100 ml./min. in the feet. A rough approximation gives the cutaneous area of the foot as equal to 55 cm.²/100 ml.[6] This would suggest average minimum flows of 3.7 ml./100 cm.²/min., and average maximum flows of 18 ml./100 cm.²/min. Their[5] smallest flow (0.5 ml./100 ml./min.) would be approximately equal to 0.9 ml./100 cm.²/min., and their largest flow (16 ml./100 ml./min.) would be equal to 29 ml./100 cm.²/min.

The observation that during body cooling the temperatures in the fingers and toes were lower than those in the more proximal portions of the extremities is similar to those reported elsewhere in the literature.[3] However, it is of considerable interest that all of the vasodilator procedures which produced maximal vasodilatation, resulted in higher cutaneous temperatures (and thermal indices) in the fingers and toes, than in the more proximal portions. Evidently the maximal flow possible in the fingers and toes is greater than in the more proximal portions of the extremities and the torso. This

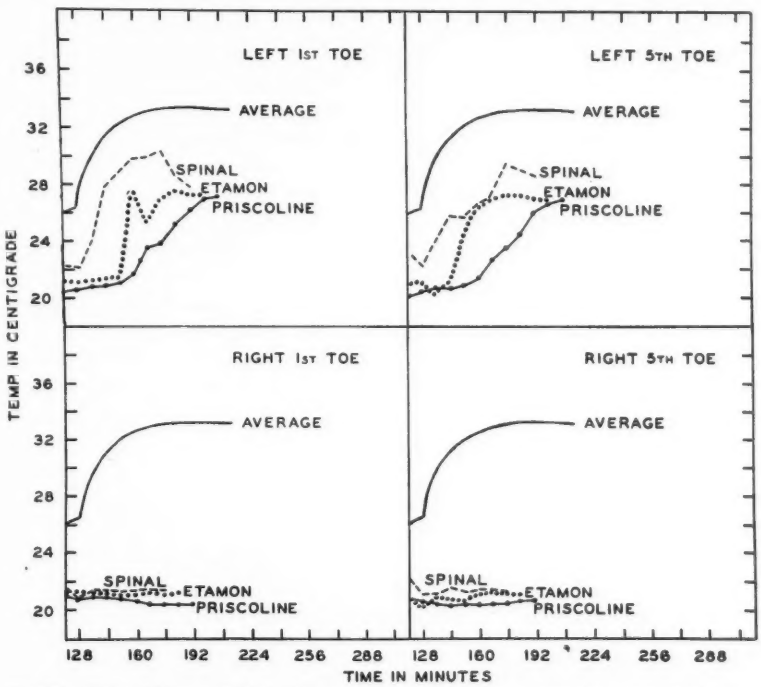

FIG. 10 (Mr. W.)—1300 mg. TEAC; 140 mg. Priscoline; 100 mg. procaine, anesthesia through T 8 on left and T 11 on right; room temperature ranged from 19.0 to 21.0 C. (average 20.1 C.).

would fit with the presence of arteriovenous channels in these regions.

Burton[3] found the maximum range for the thermal index in the toe to be 0.16 to 1.9, a 12-fold change and concluded that vasomotor reactions probably do not contribute much to the regulation of body temperature. Our findings, however, of changes of thermal circulation indices of the order of 0.06 to 4.7 (a 78-fold change) in response to body warming and cooling demonstrates to the contrary, that such vasomotor reactions must play a very prominent part in regulation of body temperature.

The magnitude of the change in heat loss per unit area of the skin is much less than the magnitude of the change in flow due to the fact that at low rates of flow much more heat is removed from each ml. of blood flowing through the skin, than is the case with higher rates of flow. The magnitude of the change of heat loss can be roughly computed by multiplying the thermal circulation index by the difference between body temperature (arterial blood temperature) and that of the skin (venous blood temperature). For an index of 0.06 (cutaneous temperature of 21 C.) the heat loss would be proportional to 0.96 (= 0.06 × 16), while for an index of 4.7 (cutaneous temperature of 34 C.) the heat loss would be proportional to 14.1 (4.7 × 3), or a 15-fold change in heat loss as compared with 78-fold change in cutaneous blood flow.

Some investigators, in discussing the use of vasodilator procedures, emphasize the change in temperature[7] or the change in blood flow.[5] However, the change that could possibly occur would be dependent on the state of initial vasoconstriction. This was frequently much less intense in previous studies than in our series. Of more importance is the maximum temperature (or thermal circulation index), i.e., the maximum blood flow reached, since this indicates the maximum flow capacity, and any reduction of this value is a measure of the degree of organic occlusion. For this reason we have omitted from our tables any reference to the change of temperature.

Our procedure of allowing one hour for cooling the body was used primarily to produce a state of strong vasoconstriction in order to see if our vasodilating procedures could overcome this degree of vasoconstriction. The results demonstrate that TEAC alone in doses approximating 20 mg./Kg. readily accomplishes this in the feet (but not the hand). Previous investigations, including our own, have been limited to 500 mg. total, and this dose has frequently failed to give maximal vasodilatation. In the hand, body warming was required with TEAC, and for both hand and foot, Priscoline required the application of body warming to produce maximal vasodilation. When so used in doses of approximately 20 mg./Kg. or 2 mg./Kg., respectively, both were satisfactory. This synergistic effect of body warming is in accord with our previous findings, and indicates the importance of keeping the patient warm and even of applying heat to the body when using these agents for their maximum therapeutic or diagnostic vasodilator effects.

The similarity of the responses to spinal anesthesia, TEAC, and Priscoline plus body warming is excellent evidence of the value of these three procedures. In addition the similarity of the results in patients with occlusive disease, we believe, demonstrates the ability of all three to prognosticate the severity of the occlusive disease and the probability of satisfactory therapy with the drugs or with surgical sympathectomy.

Our subjects expressed no preference for either TEAC or Priscoline. The degree of discomfort produced by either drug was about the same, although the symptoms were different. All subjects who took a spinal anesthesia also took either TEAC or Priscoline or both, and all preferred the drugs.

For reporting the results of our studies to the referring physician we have constructed a composite graph from the results obtained from the 20 normal subjects when body heat plus TEAC or Priscoline were used to abolish vasomotor tone in the toes (see figure 7). These curves represent the maximum and the minimum temperatures and the average temperatures reached by either the large or small toe in the 20 subjects tested. We consider that any response which produces a curve that lies outside the lower curve to have a probability of only 0.05 of being normal. Arbitrarily we have considered that: if the upper limit reached is 28–31 C., minimal occlusive disease is present;

if 24–27 C., moderate occlusive disease is present; and if below 24 C., severe occlusive disease is present. We believe that if the temperature of the toes or fingers fails to rise, interruption of the autonomic pathways by sympathectomy, paravertebral block, etc., would probably benefit the patient very little. The presence of vasospasm with or without organic disease is suggested by an unusually rapid drop in temperature in response to cooling and by delayed or incomplete response to body warming.

The dosages of TEAC described in this paper have been used on 13 patients and of Priscoline on 24 patients. These doses are somewhat higher than those reported in the literature.[5, 8, 11] However, with one exception, no alarming reactions were observed and all subjects were up and about within an hour after receiving the drugs. They complained of lassitude, listlessness, and a feeling of fatigue lasting for about two to three hours. One patient, an elderly man, with severe arteriosclerosis responded to TEAC with a marked decline in arterial pressure. He shortly developed irregular rhythm, and a shocklike state and died. Autopsy revealed a recent coronary occlusion. It was not possible to determine whether the occlusion was secondary to the marked decline in arterial pressure, whether the occlusion was fortuitous, or whether he had had an occlusion prior to the test which was not recognized by the physician in charge.

Most normal patients show little decline in arterial pressure and even a rise with either TEAC or Priscoline. However, those with severe arteriosclerosis are quite likely to show a decline with TEAC. For this reason it is mandatory to maintain a continuous check on the arterial pressure during the administration of the drug, and to stop it immediately if more than a 20 mm. Hg drop in arterial pressure occurs. In this regard, the use of intravenous administration is advantageous over intramuscular injection in that there is no delayed absorption upon cessation of administration.*

The skin temperature method of evaluating peripheral vascular diseases has several inherent disadvantages and limitations: (1) Organic occlusive disease would have to be fairly extensive to be detectable by these methods since as indicated in the section on methods a considerable decline in thermal circulation index is present before cutaneous temperature declines extensively. Thus a limited reduction in blood flow may be attended by little drop in skin temperature responses. (2) A marked drop in diastolic blood pressure (30 mm. or more) could reduce blood flow sufficiently to influence skin temperatures. (3) The procedure becomes somewhat boring and tiresome to some people because of the length of time required (about three hours).

The advantages of this method are: (1) The procedure is extremely simple to perform. (2) The results are significant in that if organic disease causes a sufficient impairment in blood flow to produce symptoms or to be functionally important, it will be revealed. (3) When severe occlusive disease is present, even small increments in blood flow in response to vasodilator procedures are readily detected. (4) The probable therapeutic effectivness of TEAC or Priscoline is revealed. (5) The dosages of the drugs used are usually well tolerated. (6) We can readily determine whether an individual's peripheral vascular disease is primarily organic or vasospastic. (7) The results are consistent, and readily reproducible.

Summary

1. In order to determine the degree of organic occlusive disease that may be present, it is necessary to determine the maximum blood flow that can exist after all neurogenic or humoral vasoconstriction is abolished. This paper is a study of methods for abolishing such vasoconstriction.

2. Blood flow was estimated from continuous records of cutaneous temperature obtained with iron-constantin thermocouples, while the subjects were kept in a room maintained at a temperature of approximately 20 C.

3. The relative blood flow was computed from the thermal circulation index (r)

* Although, except as noted above, no untoward symptoms were noted with the doses of TEAC used in these tests when given as a single injection, considerable caution must be exercised if doses of this size are contemplated for repeated injections for therapeutic purposes because of the possibility of respiratory embarrassment due to chronic accumulative toxic effects.[12]

$$r = \frac{T_s - T_a}{T_{ab} - T_s} = F_b \cdot K$$

where T_s = cutaneous temperature; T_a = air temperature; T_{ab} = arterial blood temperature; K = a constant dependent upon various factors, but principally the rate of air circulation in the room; and F_b = the rate of blood flow in the skin. Under the conditions of our experiments, the average minimal indices of 0.05 to 0.1 and average maximum indices of 4.8 were obtained for the large toe.

4. All subjects were initially exposed, lightly clad, to a room temperature of approximately 20 C. to cause maximal vasoconstriction and the skin temperature changes caused by various vasodilating procedures were recorded while the subject remained in this environment.

5. Ten normal subjects received approximately 20 mg./Kg. of body weight of TEAC alone and again with body heat. Ten normal subjects received approximately 2 mg./Kg. of body weight of Priscoline alone and again with body heat. Three of the above normal subjects also received a spinal anesthesia.

6. The results obtained with the use of TEAC plus body heat and with Priscoline plus body heat and with TEAC alone were closely comparable with those obtained by spinal anesthesia in the feet. All toe temperatures approximated the forehead temperatures. It is thus believed that the use of body heat plus TEAC or Priscoline or TEAC alone will produce practically complete inhibition of vasomotor tone in the feet. In addition, body heat plus TEAC or Priscoline caused all finger temperatures to approximate forehead temperature and it is believed that these procedures also produced practically complete inhibition of vasomotor tone here also. The use of Priscoline alone was found unreliable.

7. The average thermal circulation index in the fingers and toes obtained during the period of maximal vasoconstriction in response to body cooling was 0.06, and that during maximal vasodilation in response to the above procedures was 4.7. It is estimated that these may be approximately equivalent to flows of the order of 0.36 and of 8.7 ml./100 cm.^{2}/min., respectively.

8. The diagnostic and prognostic uses of the above procedures are discussed.

9. Certain advantages and disadvantages of these procedures are listed.

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Intermittent Reversal of Flow in a Case of Patent Ductus Arteriosus

A Physiologic Study with Autopsy Findings

By Robert E. Johnson, M.D., Paul Wermer, M.D., Marvin Kuschner, M.D., and André Cournand, M.D.

The direction of blood shunts between abnormally communicating ventricles or large vessels is dependent upon blood pressure differences in the adjacent structures, and upon the respective vascular resistance in both circulating systems distal to the communication. In a case of patent ductus arteriosus, physiologic measurements suggested that the direction of blood flow through the ductus was reversed intermittently during the systolic phase of the cardiac cycle. Pathologic studies confirmed the hypothesis by demonstrating the presence of "impingement" plaques on the aortic as well as on the pulmonary artery walls opposite the lumen of the ductus. They also gave information concerning the lesions in the pulmonary vascular bed which might be held responsible for the considerable increase in resistance, the pulmonary systolic hypertension and, attendant to it, the cyclic reversal of blood flow.

IN PATENT ductus arteriosus the direction of blood flow is ordinarily from aorta to pulmonary artery during the entire cardiac cycle. This direction of flow is determined by the higher pressure prevailing in the aorta during systole as well as diastole.

Under certain circumstances, as a late complication, this pressure relationship may be reversed, resulting in the flow of some mixed venous blood into the aorta and causing cyanosis. French clinicians have called this condition "cyanose tardive."

The following case is an example of partial reversal of flow in a patient with patent ductus arteriosus where physiologic measurements supported this diagnosis during life and were confirmed by autopsy findings.

Case Report

Clinical Data. The patient was a 42 year old woman whose heart disease was discovered following a hemoptysis at the age of 6 years. Exertional dyspnea had been present since childhood and had become severe and persistent following a pregnancy at the age of 31. She had received digitalis and mercurial diuretics for many years. Seven months before admission to the hospital, she developed ankle edema and entered another institution, where an attempt was made to ligate a patent ductus arteriosus; the operation was abandoned because of technical difficulties.

On admission to Bellevue Hospital, the physical examination revealed a small but well developed white woman who became dyspneic and faintly cyanotic on the slightest exertion. The blood pressure was 110/70. The pertinent findings were confined to the chest. The heart was enlarged both to right and left, with increased upper retrosternal dullness. A diastolic thrill was present over the entire precordium but was most intense in the third and fourth left intercostal spaces. The rhythm was regular with a ventricular rate of 90. The second pulmonic sound was impure, but louder than the second aortic sound. There was a soft apical systolic murmur (Grade II) and a harsh diastolic murmur (Grade IV) loudest in the third and fourth left intercostal spaces but heard over the entire precordium and in the interscapular region. Examination of the lungs revealed no abnormalities. The liver and spleen were enlarged. No ankle edema was present. There was no clubbing of fingers or toes.

Laboratory examinations showed a hemoglobin of 16.6 Gm. and a hematocrit of 54 per cent. A Decholin circulation time was 27 seconds, ether time 17 seconds. Venous pressure measured 120 mm. of saline. An electrocardiogram (fig. 1) revealed normal sinus rhythm with right axis deviation, diminished amplitude of T waves in Lead I, depression of the S-T segments and diphasic T waves in Leads II and III. The unipolar precordial leads were suggestive of right ventricular hypertrophy. A stethocardiogram (fig. 1) recorded simultaneously with Lead II and taken over the pulmonic area, showed abnormal vibrations during early systole

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and throughout the latter two-thirds of diastole. Chest x-ray films (fig. 2) showed marked enlargement of the pulmonary artery and its branches, enlargement of the right ventricle and either displacement posteriorly or enlargement of the left ventricle. By fluoroscopy, a "hilar dance" was demonstrated.

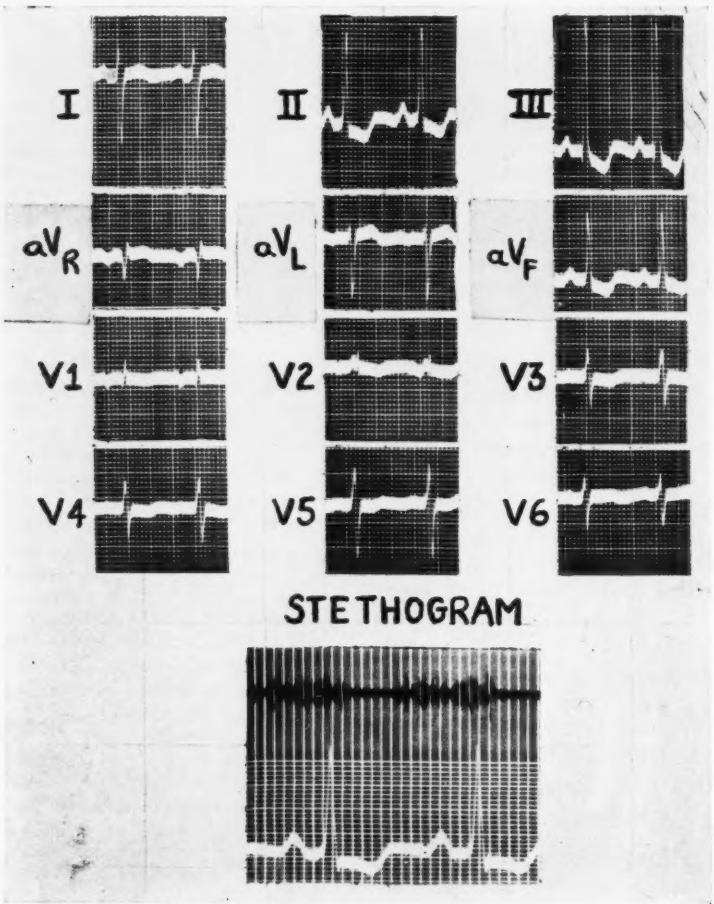


FIG. 1.—The electrocardiogram (top) and stethogram (bottom) of an adult with patent ductus arteriosus and intermittent reversal of flow. For discussion see text.

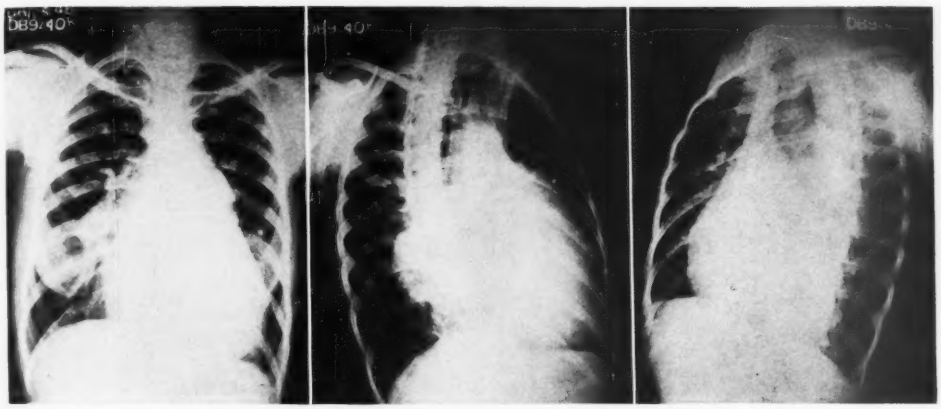
The clinical diagnosis was congenital heart disease, patent ductus arteriosus, enlarged heart, normal sinus rhythm, II B.

Physiologic Data. Table 1 summarizes the results of cardiac catheterization. Blood samples drawn from the superior vena cava, right auricle, and tricuspid area of the right ventricle were almost identical in oxygen content, indicating no intracardiac shunts in these areas. In the main pulmonary artery, however, the oxygen content was very much higher than in the right ventricle, which suggests that oxygenated blood was being added to mixed venous blood at the level of the pulmonary artery, i.e., through a patent ductus arteriosus. Since the oxygen content of the pulmonary artery blood was only 0.8 volumes per cent less than in the brachial artery, it is obvious that the catheter tip was located very near the mouth of the ductus; hence this sample represented almost entirely left ventricular blood. Unfortunately, as was first pointed out by Eppinger and associates,[1] this incompletely mixed sample precludes any accurate flow calculations through the ductus by means of the Fick equation. The finding of a higher oxygen content in the sample from the right ventricular outflow tract than in the sample from the tricuspid area was interpreted as evidence

of incompetence of the pulmonary valve. The other possibility, that of a high interventricular septal defect, was ruled out because there was no harsh systolic murmur heard over the base of the heart.

Pressure tracings were of particular interest. The systolic values of the pulmonary artery exceeded those in the systemic (brachial) artery, suggesting that, during at least part of systole, blood flow through the ductus was reversed; i.e., blood passed from the pulmonary artery into the aorta. The diastolic and mean pressures in pulmonary and brachial arteries, however, favored the usual aorticopulmonary flow.

A 91 per cent arterial saturation in the brachial artery also suggested a partial and intermittent right-to-left shunt and this was substantiated several days later with the method proposed by Burchell.[2] Oxygen saturation was determined on blood samples drawn simultaneously from the right brachial and femoral arteries and was found to be 6 per cent lower in the latter than in the former. The cause for this difference in saturation becomes apparent when one considers that, as a rule, the junction of the



a b c

FIG. 2.—Roentgenograms of the patient with patent ductus arteriosus. (a) Postero-anterior view showing generalized cardiac enlargement and marked enlargement of the main pulmonary artery and its right branch. (b) Right anterior oblique view showing enlargement of the right ventricle and the left pulmonary artery. (c) Left anterior oblique view showing displacement or enlargement of the left ventricle.

TABLE 1.—*Physiological Data in a Patient with Patent Ductus Arteriosus*

	O_2 Content (ml/liter)	Pressure (mm. Hg)		Mean
		Syst.	Diast.	
Superior vena cava	122			
Right auricle	120			3
Right ventricle (tricuspid area)	123			
Right ventricle (outflow tract)	142	135	1	
Pulmonary artery	187	132	51	83
Brachial artery	195	109	74	86
Femoral artery	180			

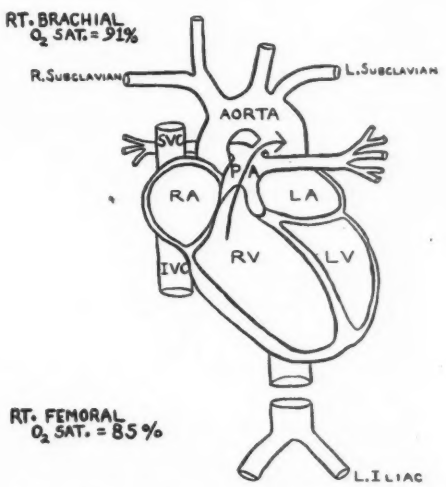


FIG. 3.—Schematic drawing illustrating the probable course of "reversed flow" through the patent ductus arteriosus (see arrow) and the anatomic relationship between the ductus and the arteries of the upper and lower extremities. For discussion see text.

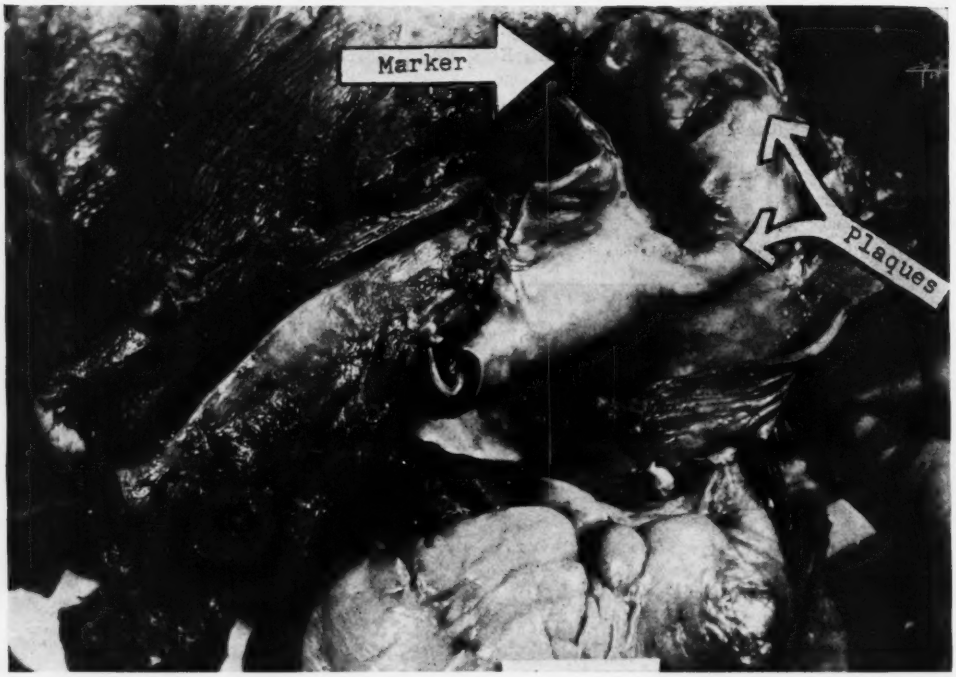


FIG. 4.—Gross specimen showing the aorta above and the heart below. The aorta has been opened to demonstrate the aortic opening of the ductus arteriosus, through which a black paper marker has been passed. The "impingement plaques" may be seen to the right of the opening.

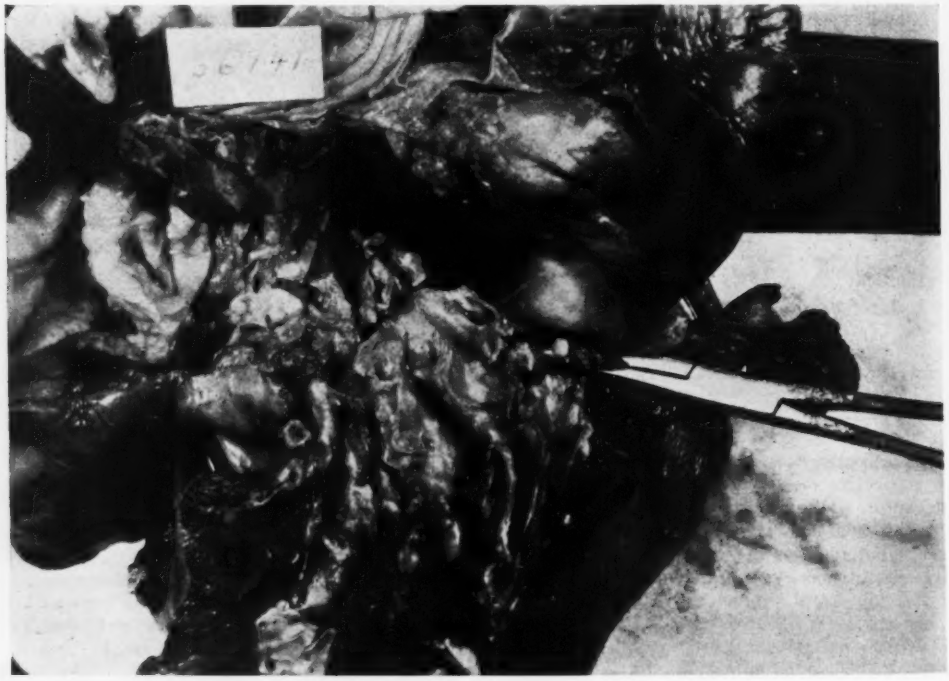


FIG. 5.—Gross specimen with a clamp attached along the right border of the main pulmonary artery. Note the numerous thick atheromatous plaques in the wall of the pulmonary artery.

ductus arteriosus and the aorta is distal to the arterial supply of the upper extremities (fig. 3). Therefore, of the mixed venous blood which is "reversed" into the aorta, a greater proportion will enter the descending aorta than will enter the vessels to the upper extremities. Hence, the arterial oxygen saturation of blood from the femoral artery will be lower than that from the brachial.

impossible to section the ductus. Closure was attempted by tightening two ligatures of umbilical tape around the ductus, following which the thrill could no longer be felt. However, postoperatively, the murmurs previously heard were still present. On the fifth postoperative day, death occurred shortly after a blood transfusion.

Pathologic Report. Pertinent autopsy findings were

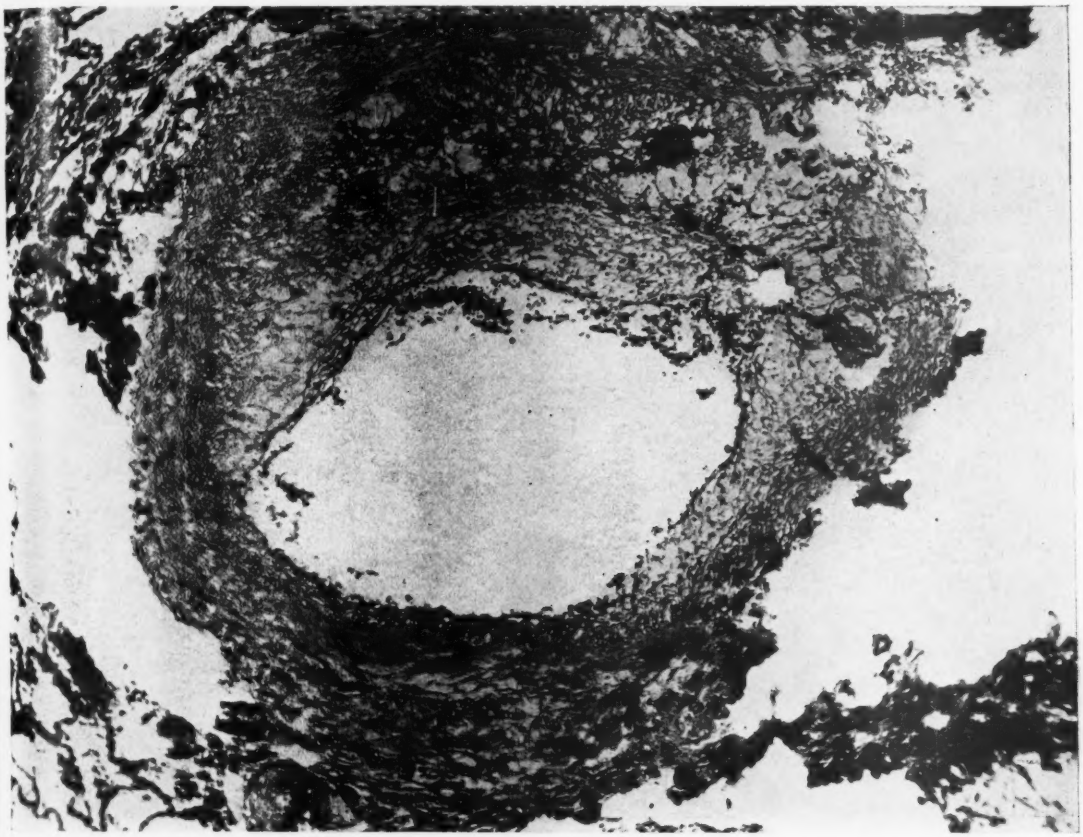


FIG. 6.—Photomicrograph of a section of a medium sized branch of the pulmonary artery. Note the eccentric narrowing of the lumen by the accumulation of large numbers of lipid-laden macrophages in the intima, an early atheromatous change.

It was suspected clinically that the extreme hypertension of the pulmonary artery might have been due in part to pulmonary arteriolar sclerosis.

The patient underwent surgery for the second time a few weeks after the physiologic studies. A very wide patent ductus arteriosus of the "window type" was found. Considerable difficulty was encountered in isolating and freeing the ductus because of the surrounding scar tissue from the previous operation. Due to technical difficulties, it was

confined to the heart and lungs. The right auricle was not enlarged. There was marked hypertrophy and dilatation of the right ventricle, the wall of which measured 7–11 mm. in thickness. Microscopically, the right ventricle showed focal fibrosis and hypertrophy. The left ventricle was not grossly enlarged and its wall measured 12–15 mm. in thickness. A very large ductus arteriosus was present which had no measurable length, as it existed almost as a side-to-side anastomosis between the aorta and the

pulmonary artery. The ductus was patent with an internal diameter of 5 mm., although the ligatures were still in place. Following removal of the ligatures the internal diameter measured 10 mm. The aorta measured 7.5 cm. in circumference and showed minimal atherosclerosis except for three large discrete plaques which were located just opposite the aortic opening of the ductus. These have been called "impingement plaques" (see fig. 4), and are presumably due to the high velocity of the jet of blood from the patent ductus striking the wall of the vessel. The pulmonary artery was greatly enlarged, its circumference measuring 10.0 cm. There was marked atherosclerosis of the walls of the pulmonary artery and all of its branches which could be examined grossly (see fig. 5). On the wall of the main pulmonary artery, opposite the pulmonic opening of the ductus, there were lesions which resembled the "impingement plaques" described above.

Microscopically, the pulmonary arteries showed marked atherosclerosis with large numbers of cholesterol-laden macrophages in the intima (fig. 6). Van Gieson stain on these vessels revealed a fraying out and rupture of the elastic tissue of the media at focal points along the vessel wall with aneurysm-like bulging of the intima at such points (fig. 7). Throughout the lungs the small arteries and arterioles showed moderate to marked thickening of their walls, due to intimal proliferation and medial hypertrophy (fig. 8).

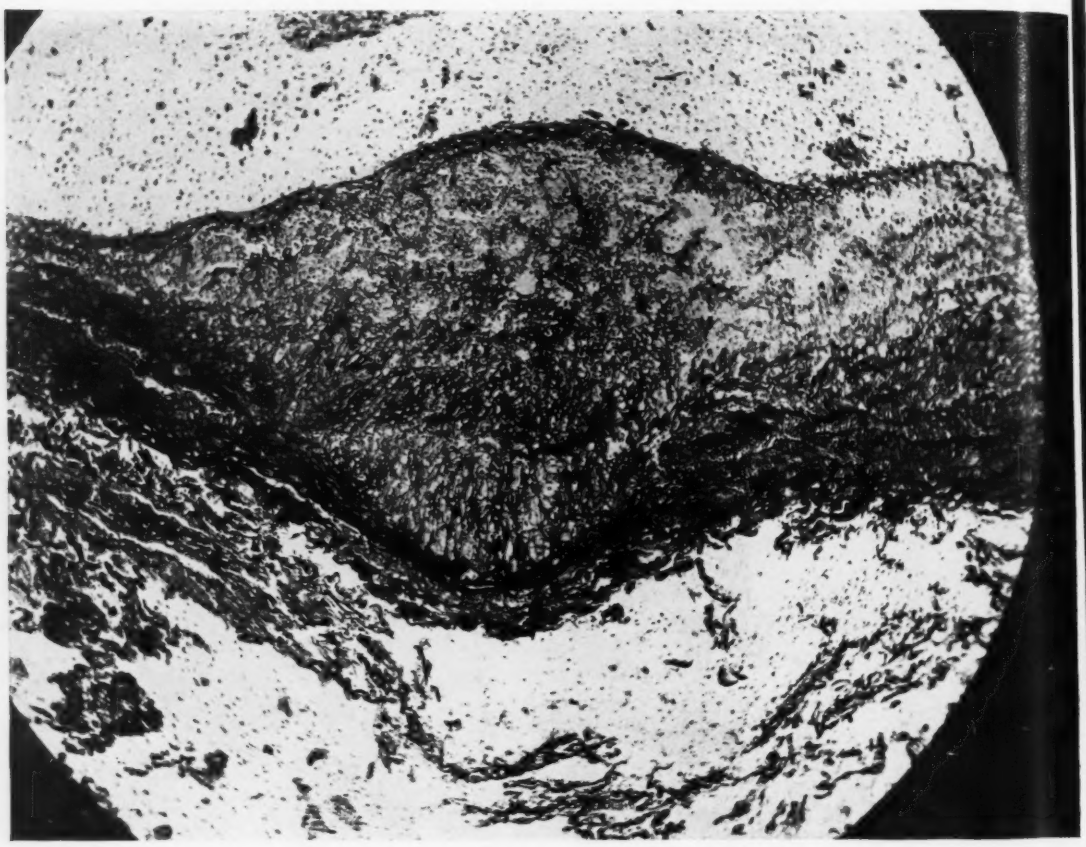


FIG. 7.—Photomicrograph of a medium sized branch of the pulmonary artery. (Elastic tissue—Von Gieson stain.) There is a marked atherosclerosis with extensive deposition of lipid in the intima. Of particular interest is the rupture of the elastic fibres of the media with bulging of the vessel wall and extrusion of intima in aneurysmal fashion.

DISCUSSION

From the physiologic data and pathologic findings, notably the presence of "impingement

plaques" on the aortic wall opposite the ductus, it can be concluded that this patient, probably late in her disease, had an intermittent, partial reversal of flow through the ductus arteriosus. It is most likely that the marked pulmonary hypertension was the major factor responsible for this reversal. It has been emphasized that under resting conditions the pulmonary artery pressures in patent ductus arteriosus may remain normal. However, many investigators[2–6] have described pulmonary hypertension in patients with this defect. The cause for the hypertension is not definitely known. It is unlikely that the increased blood flow alone is responsible unless it reaches at least three times the normal pulmonary flow.[7] However, if this value is exceeded, pulmonary hypertension may occur. It has not yet been proved, however, whether a very large and sustained pulmonary blood flow will produce pulmonary vascular sclerosis. The latter possibility is not supported by the data of Welch and Kinney,[8] who did not find any increase in pulmonary vascular sclerosis in any of the 25 patients with a large patent ductus arteriosus. However, these authors assumed the presence of a large pulmonary blood flow solely on the basis of the large size of the aorticopulmonary connection. They stress the presence of sclerosis of the pulmonary vascular tree in all patients over the age of 40.

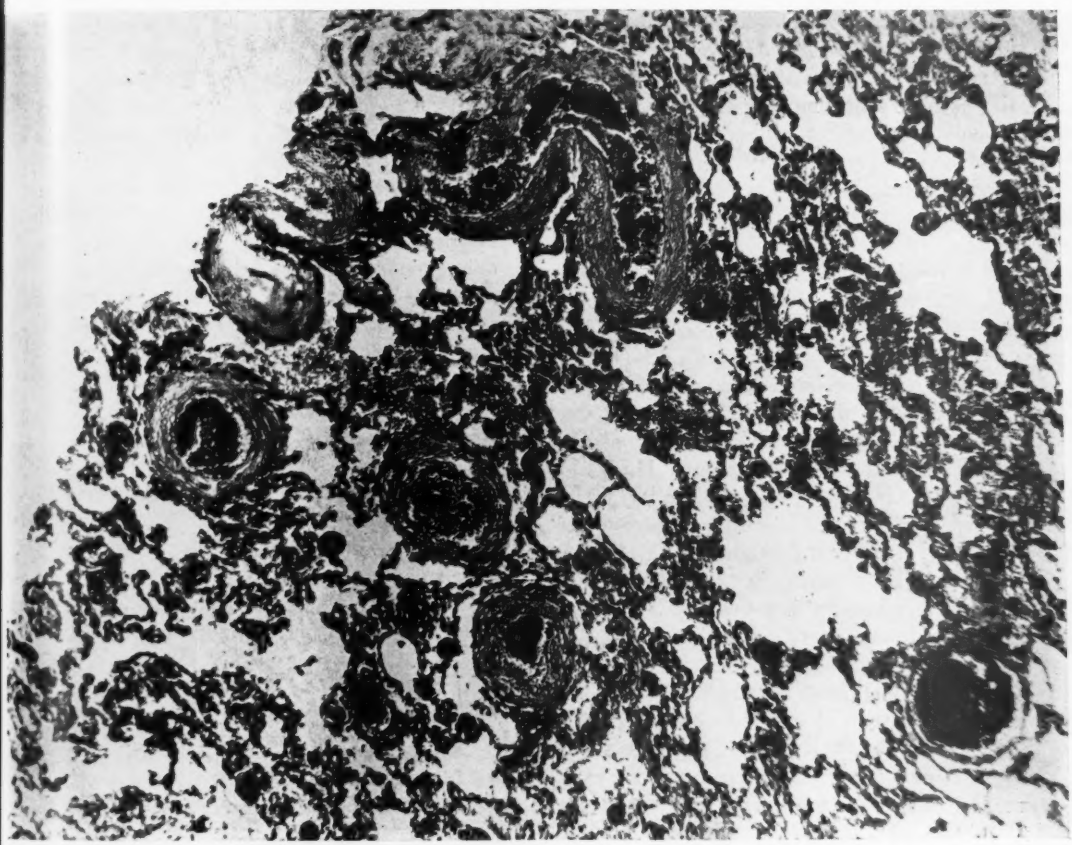


FIG. 8.—Photomicrograph of a section through the lung. Note the intimal and medial thickening of the walls of small arteries and arterioles. This change was present throughout both lungs.

In the patient here reported it may well be that the prolonged increase in pulmonary blood flow eventually resulted in pulmonary hypertension. As she grew older, marked sclerotic changes may have occurred in the pulmonary arterioles, largely as a result of the aging process, and pulmonary vascular resistance was thus further increased, leading to an increase in pulmonary hypertension. It has been recently stressed[9] that, in patients having a communication between the pulmonary and systemic circulations, the proportion of blood shunted through one or the other circulation is dependent upon the resistance of the peripheral arteriolar bed on one side, the local resistance at the site of the anomolous communication and the resistance of the pulmonary vascular bed distal to it on the other. As the pulmonary hypertension increased over the years, the aorticopulmonary shunt through the ductus may well have decreased gradually and hence, the final blood flow may not represent the maximal flow present in earlier years. The findings in this case serve to expand Hamilton's concept[9] by indicating the relationship of increased pulmonary vascular resistance to temporary reversal of flow through the ductus. Pulmonary hypertension in this patient probably not only resulted in decreasing the left-to-right shunt but served to initiate the intermittent right-to-left shunt.

The question may be raised as to whether the ductus arteriosus should be ligated in the presence of a partial reversal of flow associated with atherosclerotic changes in the pulmonary vessels. Since the increased pulmonary blood flow doubtless plays a role in the production of pulmonary hypertension, ligation of the ductus which would result in a marked reduction of both the pulmonary blood flow and pulmonary hypertension, would appear to be beneficial, even under these circumstances.

The finding of a reduction of blood oxygen saturation in the femoral artery as compared to that in the brachial artery is not pathognomonic of intermittent reversal of flow in a patent ductus arteriosus. Similar findings have been postulated by Taussig[10] in cases of coarction of the aorta of the infantile type with hypoplasia of the ascending aorta, overriding of the interventricular septum by a pulmonary artery communicating with the descending aorta through a patent ductus arteriosus. It should be mentioned that in the presence of such a syndrome, the total systemic flow cannot be calculated with the Fick principle. Even though venous blood samples might be obtained separately in the superior and inferior vena cava, the unknown quantity of oxygen consumption in each separate system makes even an approximative value for total systemic flow unreliable.

Summary

1. A case of patent ductus arteriosus, with intermittent reversal of flow through the ductus, is reported in an adult woman.

2. The intermittent reversal of flow was demonstrated during life by pressure measurements in the pulmonary and the systemic circulations, and by blood oxygen values in blood samples drawn simultaneously from right brachial and femoral arteries.

3. Pathologic findings following postoperative death supported the diagnosis by demonstrating "impingement plaques" on the aortic wall around the mouth of the patent ductus arteriosus.

4. The physiologic mechanisms leading to reversal of blood flow are discussed.

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Acute Coronary Insufficiency Due to Acute Hemorrhage: An Analysis of One Hundred and Three Cases

By Arthur M. Master, M.D., Simon Dack, M.D., Henry Horn, M.D., Bernard I. Freedman, M.D., and Leonard E. Field, M.D

The occurrence of 59 cases of acute coronary insufficiency among 103 patients with acute hemorrhage, chiefly from the gastrointestinal tract, emphasizes the frequency and gravity of this generally unrecognized complication of bleeding. Clinical, electrocardiographic and anatomic manifestations of myocardial ischemia and subendocardial necrosis are prone to appear in previously diseased hearts, although they may develop in otherwise normal hearts. Consequently, prompt and adequate blood replacement is required in patients with coronary arteriosclerosis, enlarged hearts, valvular heart disease, etc. to prevent as well as to treat coronary insufficiency secondary to hemorrhage.

THE CONCEPT of acute coronary insufficiency has become well established on the basis of clinical and pathologic observations.[1–13] It has been shown that myocardial ischemia results from a disproportion between the oxygen requirements of the myocardium and the coronary blood flow, and is provoked by factors which either increase the work of the heart, decrease coronary blood flow or decrease the quantity of oxygen carried by the blood. When cardiac ischemia is severe or protracted, myocardial necrosis may develop in the absence of acute coronary occlusion. The necrosis following acute coronary insufficiency is focal, disseminated and usually localized to the subendocardial region of the left ventricle, especially within the papillary muscle. The electrocardiogram is characterized by the presence of RS-T segment depression and T-wave inversion in one or more leads and often in all leads. These changes are usually transient and disappear rapidly following subsidence of the ischemia. Deep Q waves and elevations of the RS-T segment almost never occur, thus differentiating this condition from massive infarction due to acute coronary artery occlusion.[10]

The clinical factors which may lead to acute coronary insufficiency have been enumerated previously.[11] We have found hemorrhage to be one of the most frequent and important precipitating causes of acute coronary insufficiency. In a patient whose coronary circulation is already impaired by arteriosclerosis or by cardiac hypertrophy, hemorrhage from any source offers dangerous potentialities. It is not sufficiently appreciated that bleeding is important not only because of loss of an essential transport agent for oxygen and food but also because of the cardiac damage which may ensue.

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Material and Results

This report is based on a clinical analysis of 103 consecutive cases of moderate or severe hemorrhage admitted to the Mount Sinai Hospital. Included in the series were those patients in whom evidences of hemorrhage were considered to be of sufficient degree to require treatment and from whom one or more electrocardiograms were made during the bout of hemorrhage.

The gastrointestinal tract was the source of bleeding in 95 patients, the uterus in 4, the prostate gland in 2, and a ruptured aorta in 2. The most common etiologic factor for massive gastrointestinal hemorrhage was peptic ulcer (64 cases). Less common causes were esophageal varices (10 cases), ulcerative colitis (8 cases) and hemorrhoids (8 cases).

The clinical course of each patient was studied with particular regard to the amount and rapidity of hemorrhage, hemoglobin level, heart rate, blood pressure, presence of shock, and the electrocardiographic findings. The 103 cases were divided into two general groups. Group I consisted of 59 cases (57 per cent) with clinical or electrocardiographic signs of acute coronary insufficiency. Group II comprised 44 cases (43 per cent) with neither clinical nor electrocardiographic evidence of coronary insufficiency. Group I could be subdivided into 32 cases with an electrocardiographic pattern of acute coronary insufficiency but no clinical stigmata, 6 cases with clinical findings of coronary insufficiency but normal electrocardiograms and 21 instances

with both clinical and electrocardiographic abnormalities.

Twenty-two patients died of the effects of the hemorrhage; of these, 18 presented clinical or electrocardiographic signs of acute coronary insufficiency. Four of the 13 autopsied cases presented cardiac alterations characteristic of acute coronary insufficiency; namely, myocardial necrosis in the absence of recent coronary artery occlusion.

Discussion

Clinical, Electrocardiographic and Anatomic Features

Clinical Signs of Coronary Insufficiency. Clinical signs of acute coronary insufficiency were noted in 27 patients, in 21 of whom acute electrocardiographic changes were observed. The electrocardiogram in the other 6 remained unaltered. Precordial or substernal pain occurred in 15 cases, congestive heart failure developed in 8, and both pain and cardiac failure together appeared in 3 instances.

The precordial pain often resembled that seen in coronary artery disease. In 6 patients, severe precordial pain in association with shock, tachycardia and drop in blood pressure which followed the hemorrhage closely simulated acute coronary artery occlusion. Indeed, this diagnosis was entertained not infrequently before it was recognized that precordial pain could be a manifestation of acute coronary insufficiency precipitated by hemorrhage.

Heart failure during or following hemorrhage was observed in 11 cases and was manifested by dyspnea, pulmonary congestion or edema, peripheral venous engorgement and gallop rhythm. Acute pulmonary edema of sudden onset was not uncommon and constituted still another feature which caused the clinical picture to resemble that of acute coronary artery occlusion.

Precordial pain and heart failure occurred, as a rule, in the patients with severe acute anemia or shock. The average hemoglobin level in these cases was 44 per cent (Sahli), while the actual drop in hemoglobin averaged 37 per cent from control levels. Similarly, shock, together with a marked fall in blood pressure and tachycardia, occurred in over two-thirds of the patients (69 per cent).

The precordial pain and the heart failure were generally transient, subsiding as the hemorrhage ceased or was actively treated and as the shock diminished and the blood hemoglobin rose toward normal levels, usually after one or more transfusions. The response to treatment was particularly striking in several cases of recurrent hemorrhage in which each bout of blood loss had precipitated an episode of severe angina pectoris. It was significant that angina pectoris was absent or mild in the periods between the occurrence of hemorrhage, and in each instance subsided rapidly following active treatment of the bleeding.

Electrocardiographic Findings. Significant acute changes in the electrocardiogram were present in 53 of the 103 patients. These consisted generally of flattening or inversion of the T wave, with or without depression of the RS-T segment. Abnormal T waves alone were observed in 24 cases, RS-T depression alone in 4 and combined RS-T and T changes in 25 cases. The mortality rate of the 24 cases showing T-wave changes alone was only 17 per cent as compared with a rate of 40 per cent in the 25 patients who had presented RS-T depression in association with T-wave changes. It seems, therefore, that a combination of RS-T segment depression and T-wave inversion represents a more profound degree of coronary insufficiency than a change in the T wave alone. There were but 4 patients in whom changes were limited to the RS-T segment, and 3 of these patients died (fig. 1).

The most common lead combinations showing the RS-T and T wave changes were I, II and IV; I, II and III; and I, II, III, IV; respectively. Abnormalities were disclosed most frequently in Leads I and II.

The T-wave changes consisted of flattening and partial or complete inversion. The RS-T segment was depressed from 0.5 to 2.0 millimeters. RS-T elevation was observed infrequently in Lead III but never in any of the other leads. Deep Q waves were also extremely rare and developed in but 3 cases. Occasionally a deep Q wave was present prior to the episode of hemorrhage, and was the result of infarction due to a former coronary artery occlusion. The relative rarity of RS-T elevation and deep Q waves was of aid in differentiating the electro-

cardiogram of acute coronary insufficiency from that of myocardial infarction due to acute coronary artery occlusion.

Influence of Sex and Age. The series included 78 men and 25 women. Forty-one of the former (53 per cent) and 18 of the latter (72 per cent) developed evidence of acute coronary insufficiency. The mortality rate in each sex group was exactly the same.

The ages of the patients with hemorrhage who developed acute coronary insufficiency varied greatly (from 18 to 79 years). Similarly, the

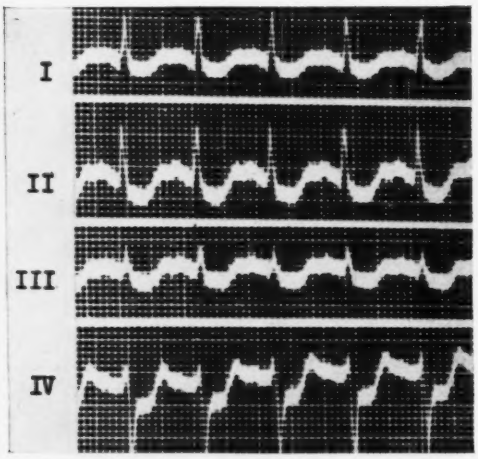

FIG. 1—L. F., a man of 54 years with no antecedent cardiac disease. Profuse gastrointestinal bleeding produced shock, severe acute coronary insufficiency, myocardial ischemia and death. The electrocardiogram the first day of the hemorrhage disclosed pronounced RS-T depressions in all leads; no digitalis had been given.

ages of those without coronary insufficiency ranged from 22 to 89 years. It appeared that age itself did not significantly influence the incidence of acute coronary insufficiency in this series. Acute coronary insufficiency developed, not infrequently, in the very young if the hemorrhage was sufficiently severe or protracted. Thus, one instance of myocardial necrosis was observed in a girl of 19 in whom the coronary arteries were perfectly normal. On the other hand, some of the elderly patients presented no significant signs of coronary insufficiency even after fairly severe hemorrhage. The average age of the men who developed coronary insufficiency was 52, and that of the women was 45 years.

Antecedent Cardiac Disease. Antecedent cardiovascular disease proved to be a more significant factor than age in the occurrence of coronary insufficiency following hemorrhage. Thirty-eight of the 103 patients presented clinical or electrocardiographic evidence of previous cardiovascular disease, generally of the hypertensive or arteriosclerotic variety. Seventy-one per cent of these 38 patients developed acute coronary insufficiency as compared with an incidence of 49 per cent in the group without preceding cardiovascular disease. Further analysis revealed that the association of antecedent cardiovascular disease was approximately twice as great in the coronary insufficiency group (47 and 25 per cent, respectively). These observations indicate that chronic coronary insufficiency incident to coronary arteriosclerosis or cardiac hypertrophy renders the heart more vulnerable to the hemodynamic effects of hemorrhage.

Blood Hemoglobin Level. The blood hemoglobin concentration at the time that the clinical or electrocardiographic signs of coronary insufficiency had developed were tabulated and the actual decrease in hemoglobin determined by comparison with the level prior to the hemorrhage or following recovery. The average hemoglobin concentration for the group with evidence of coronary insufficiency was 54 per cent of normal (Sahli). That of the noncoronary insufficiency group was 63 per cent. When only those cases were considered in which symptoms of coronary insufficiency had developed, the average hemoglobin level was found to have been 44 per cent of normal. The number of patients who had sustained a drop in hemoglobin level of 20 to 30 per cent or more was distinctly greater in the coronary insufficiency group. Conversely, it was found that when the hemoglobin level had decreased 30 per cent or more, acute coronary insufficiency appeared in four-fifths of the patients.

In general, therefore, acute coronary insufficiency occurred when the hemorrhage effected a significant drop in blood hemoglobin. Nevertheless, acute coronary insufficiency was noted, not infrequently, before any significant anemia

had developed and, occasionally, even if such had never appeared. Thus, severe precordial pain associated with acute electrocardiographic changes occurred in 3 patients whose hemoglobin level dropped only 10 per cent or less. In these patients the hemoglobin level might not have been an accurate measure of the severity of hemorrhage because of hemoconcentration. It is evident, accordingly, that acute anemia is an important but not an essential force for the production of acute coronary insufficiency in hemorrhage. In the absence of anemia, the factors of shock, drop in blood pressure and tachycardia take on additional importance in precipitating coronary insufficiency.

The electrocardiogram seemed to be a sensitive indicator of the intensity of bleeding. Alterations in the electrocardiogram often were noted long before clinical manifestations of coronary insufficiency appeared and in some cases even when other clinical signs were wanting.

Blood Pressure. The average fall in blood pressure at the time the electrocardiogram was obtained was 27 mm. Hg in the coronary insufficiency group as contrasted with only 9 mm. in the group without signs of coronary insufficiency. Further, one-third of the former had shown a drop in blood pressure of 40 mm. or more as compared with only 5 per cent of the latter group. A significant drop in blood pressure following a bleeding episode proved to be an important precipitating factor of coronary insufficiency. This belief is supported by the observation that the incidence of coronary insufficiency was 84 per cent when the blood pressure fell 20 mm. or more and 90 per cent when the fall was 40 mm. or more. A drop in blood pressure was thus directly related to the presence of coronary insufficiency as indicated by electrocardiograms and by clinical signs.

Tachycardia. Tachycardia of 100 beats or more per minute was noted in 52 per cent of the patients with coronary insufficiency and in only 14 per cent of the other group. Conversely, 82 per cent of the patients with heart rates of 100 or more manifested stigmata of coronary insufficiency. Evidence of coronary insufficiency was noted in the 10 instances (17 per cent of the group) in which the heart rate rose to 125 or more. Such a rapid rate never occurred in those patients without signs of myocardial ischemia.

In the coronary insufficiency group, tachycardia generally accompanied a marked drop in blood pressure. Although tachycardia represents a compensatory mechanism for the maintenance of cardiac output following blood pressure fall, the combination of hypotension and tachycardia apparently led more readily to the development of coronary insufficiency.

Shock. Clinical manifestations of shock (syncope, prostration, feeble pulse, clammy skin, etc.) were observed in 58 per cent of the coronary insufficiency group but only in 20 per cent of Group II. The incidence of shock was found to be as high as 69 per cent in the 27 patients with signs of coronary insufficiency. Moreover, of the 43 patients who developed signs of shock, 79 per cent manifested myocardial ischemia. These figures emphasize the close relationship between shock and coronary insufficiency following hemorrhage. The coexistence of a fall in blood pressure and tachycardia was noted frequently in the majority of patients with shock. As one would expect, shock was more common in the patients with coronary insufficiency who succumbed (82 per cent) than in those who recovered (48 per cent).

In summary it can be said that a fall in blood hemoglobin and blood pressure, tachycardia and shock are all significant forces in precipitating coronary insufficiency following hemorrhage. When the bleeding episodes were accompanied by any one or more of these clinical findings, acute coronary insufficiency developed in at least four out of every five cases.

A typical example of coronary insufficiency is illustrated in the following case.

Case 2.—H. C., a 38 year old man with a duodenal ulcer, was hospitalized because of a moderate gastrointestinal hemorrhage of two weeks' duration. For one week prior to entry he had experienced dyspnea and squeezing precordial pain which had radiated to the left shoulder and arm following exertion. Hypertension had been present for eight years with no diminution of cardiac reserve; blood pressure varied between 150–170 mm. systolic and 100–110 mm. Hg diastolic.

Upon admission, July 19, 1941, there was no shock, tachycardia or fall in blood pressure. The hemoglobin level was 65 per cent. The electrocardio-

gram (fig. 2), July 21, showed inversion of the T wave in Leads I, II, and III. With cessation of the bleeding and as the hemoglobin level rose, angina pectoris disappeared and the electrocardiogram showed a gradual return to normal. On July 23 the hemoglobin was 74 per cent; the electrocardiogram disclosed the T wave to be low in Leads I and II and upright in Lead III. On July 28, the hemoglobin was 78 per cent while the electrocardiographic pattern was normal. Subsequent to discharge from the hospital, the 2-step test electrocardiogram was also normal.

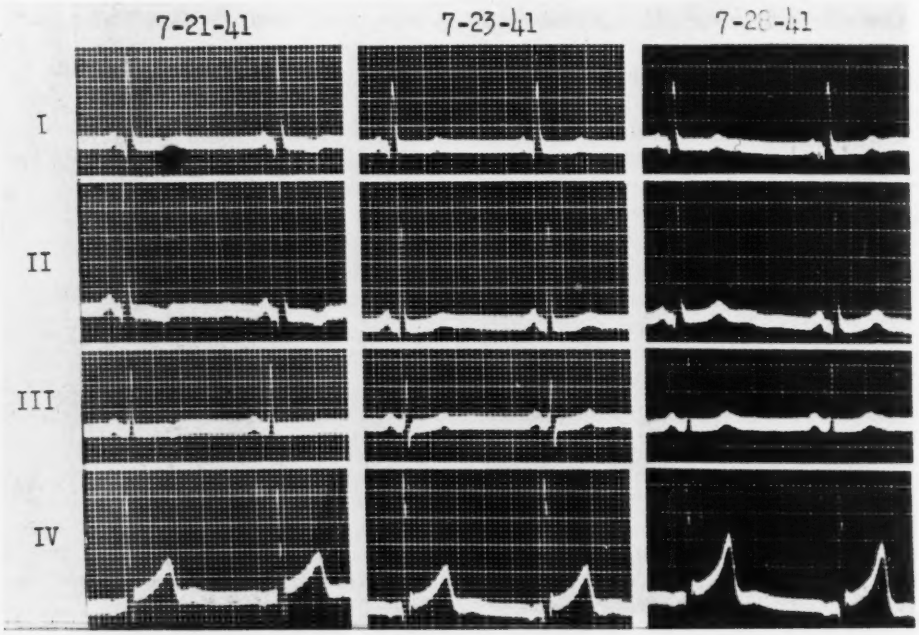

FIG. 2.—H. C., a man of 38 years. Transient anginal syndrome and acute coronary insufficiency during gastro-intestinal hemorrhage. Hemoglobin fell only to 65 per cent. Upon admission to hospital, July 21, 1941, the T wave in Leads I, II, and III was inverted; normal within a week.

Comment: A case of acute coronary insufficiency with clinical and electrocardiographic manifestations occurring in a hypertensive man during the course of a moderately severe and protracted gastrointestinal hemorrhage. Following treatment of the anemia, there was rapid disappearance of angina pectoris and restoration of the electrocardiogram to normal.

Anatomic Findings. The myocardium in patients with coronary insufficiency due to acute blood loss presents a pathologic picture similar to that seen in instances of acute coronary insufficiency due to other causes.[14] The degree of morphologic changes depends upon the severity and rapidity of the hemorrhage and the nature of the underlying predisposing factors.[13] Following acute severe hemorrhage, the myocardium of patients with coronary arteriosclerosis, cardiac hypertrophy or aortic valvular disease, for example, will be more seriously affected than that of a patient with no previous heart disease. The rate of blood loss, duration of the anemia, degree of associated shock, work of the heart, and other factors previously discussed, directly influence the alterations in the cardiac musculature.

The myocardial ischemia that occurs after acute blood loss, however, may be mild and transient, and anatomic lesions entirely absent. In more protracted instances, on the other hand, focal subendocardial microscopic lesions become apparent. These may vary from tinctorial changes in the muscle fibers, loss of striations, smudginess of fibrillar outline and

nuclear degeneration to actual necrosis with reactive cellular infiltration. Finally, in the most pronounced cases, confluent zones of subendocardial necrosis are grossly recognizable.

Thirteen cases came to autopsy, but only 7 hearts were available for re-examination by the writers. These included all 4 positive cases and 3 of the negative cases. All grossly visible coronary arteries were studied by transverse sections at intervals of 2 to 3 mm. In no instance was an acute coronary artery occlusion found. Microscopic studies were made routinely from all representative portions of heart wall; namely, anterior, posterior and lateral walls, septum, apex, anterior and posterior papillary muscles of the left ventricle, anterior and posterior walls of the right ventricle, and auricles when indicated. In addition, any area disclosing discoloration or mottling was examined histologically.

The variety of cardiac lesions may be noted in the following illustrative cases.

Case 3.—H. S., a 67 year old woman with clinically recognized aortic stenosis presented the most extensive myocardial changes we have observed, in the absence of an acute coronary artery occlusion, following gastrointestinal hemorrhage. Since 1940 the patient had experienced angina pectoris precipitated by repeated bouts of gastrointestinal hemorrhage. During these periods the blood hemoglobin level dropped to 40–50 per cent, and the electrocardiogram would disclose pronounced RS-T segment depression and T-wave inversion (fig. 3, *A*). When the hemoglobin rose above 60 per cent following therapy, the angina pectoris subsided and the electrocardiogram would improve. The patient was again hospitalized on November 1, 1942, because of gastrointestinal bleeding for eight days and precordial pain for four days. Her blood pressure upon entry was 90/60, pulse rate 120 and hemoglobin 42 per cent. On the following day she suddenly developed the clinical picture of shock and pulmonary edema and died. The electrocardiogram disclosed a supraventricular tachycardia of 170; marked RS-T depression in Leads I, II and IV; and a deep Q_3.

Cardiac Findings: The heart weighed 575 grams and was dilated. The left ventricle was moderately hypertrophied. Widespread necrosis was noted grossly in all portions of the left ventricle, including the papillary muscles. The zone of necrosis involved the inner third of the thickness of the ventricular wall, while the outer two-thirds of the wall, including the epicardium, were intact. The endocardium itself appeared normal, and no mural thrombi were observed. The affected areas disclosed yellowish mottling with scattered red foci, the latter especially noticeable within the septum and posterior wall. The right ventricle showed merely slight fatty infiltration.

The aortic valve was rigidly thickened, irregularly nodular and calcified; the aortic orifice severely stenotic. The mitral valve leaflets were moderately thickened; the mitral ring was markedly calcified. The coronary ostia were patent. The left circumflex coronary artery and its branches to the anterior left ventricle were moderately narrowed by arteriosclerotic plaques, while the remaining major branches of the coronary arteries disclosed only slight mural thickening. Detailed transverse sectioning of the entire coronary artery tree revealed no evidence of either a recent or old occlusion.

The microscopic picture was similar in all the involved regions (fig. 3, *B*). The endocardium was unaltered. Disseminated focal and often confluent areas of myonecrosis were present in the subendocardial layer, among which many islands of normal heart muscle remained. Frequently a very thin strip of uninvolved muscle was interposed between the endocardium and the zone of myonecrosis. The altered portions of myocardium disclosed hemogenization, loss of striations, tinctorial changes, karyolysis, loss of nuclei, and conspicuous necrosis of muscle fibers. Interspersed were foci of hemorrhage and scattered cellular infiltrates consisting of polymorphonuclear leukocytes, lymphocytes and histiocytes.

The anatomic diagnoses were: acute, widespread, focal and confluent subendocardial necrosis of left ventricle; inactive rheumatic aortic and mitral valvulitis with severe aortic stenosis and moderate mitral stenosis and insufficiency; moderate coronary arteriosclerosis with narrowing of the lumen.

Comment: A patient in whom angina pectoris occurred during episodes of gastrointestinal bleeding developed extensive subendocardial necrosis of the myocardium. Rheumatic cardiovalvular disease, as well as coronary arteriosclerosis, acted as predisposing factors. Hemorrhage, with resulting hypotension, tachycardia and shock, occurred and precipitated acute coronary insufficiency.

Case 4.—S. S., a 60 year old man was observed in two bouts of severe hematemesis due to a chronic peptic ulcer. The first episode occurred on September 10, 1945, and was accompanied by shock, a blood pressure of 80/40, pulse rate of 120, poor heart sounds and hemoglobin of 30 per cent. The electrocardiogram on the day after admission showed semi-inversion of the T wave in Leads I and IV. On September 19, following several transfusions, the tracing was normal. In the second bout of hemorrhage, which took place on January 17, 1946,

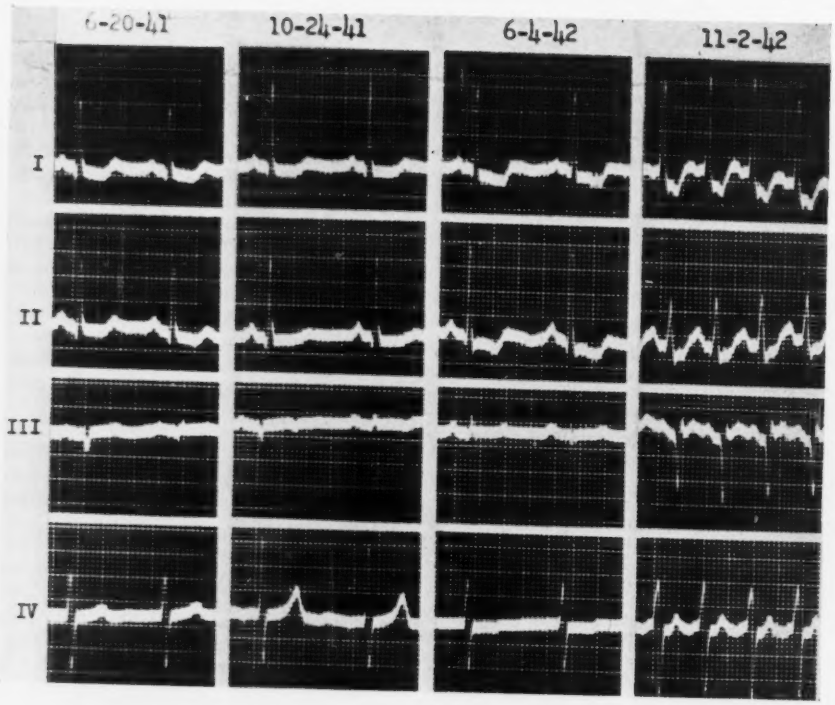

FIG. 3A

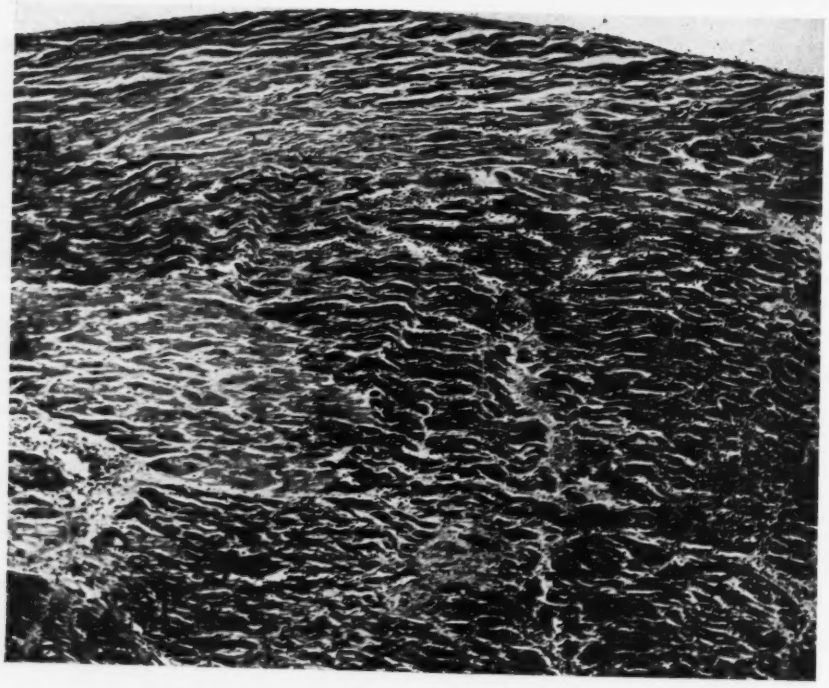

FIG. 3B

there was shock with a blood pressure of 90/50, tachycardia, poor heart sounds and a hemoglobin of 23 per cent. An electrocardiogram on January 21 revealed a low T wave in Lead I (fig. 4). On January 26 the patient developed agonizing substernal pain, dyspnea, cyanosis and severe shock and died within several hours. Electrocardiograms during this episode disclosed depression of the RS-T segment in Lead IV.

Cardiac Findings: The heart weighed 450 grams. Slight hypertrophy of the left and slight dilatation of both ventricles were noted but there were no gross myocardial changes. Moderate thickening of the mitral and tricuspid leaflets and slight thickening of the aortic cusps were present. The coronary ostia were patent. Slight to moderate arteriosclerosis was noted in the greater portion of the coronary artery tree. However, no narrowing of the lumen was evident; in fact, the lumen of the anterior descending branch of the left coronary artery was

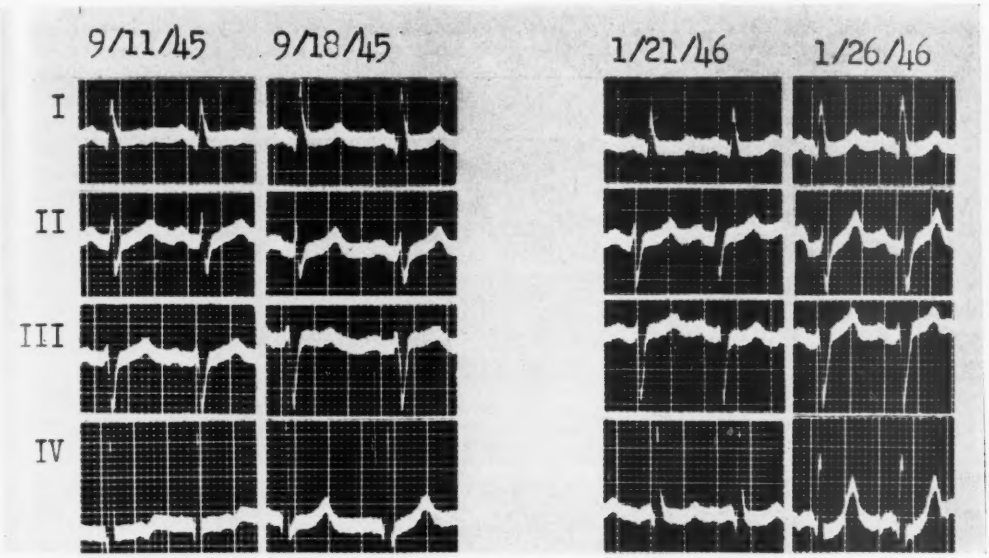

FIG. 4.—S. S., a man of 60 years with two bouts of hematemesis resulting from peptic ulcer. At autopsy, moderate coronary arteriosclerosis and acute, focal, subendocardial necrosis in both papillary muscles and posterior wall of left ventricle. On September 11, 1945, the hemoglobin was 30 per cent; the electrocardiogram disclosed inversion of the T wave in Leads I and IV. Following transfusions, clinical recovery and normal electrocardiogram resulted. On January 21, 1946, following hematemesis with shock and hemoglobin of 23 per cent, the electrocardiogram showed the T wave low in Leads I and IV. Five days later, the patient experienced agonizing substernal pain, and the RS-T segment was depressed in Lead IV; death followed.

FIG. 3.—H. S., a 67 year old woman with antecedent aortic and mitral valve disease, as well as coronary artery disease. Recurrent episodes of gastrointestinal bleeding precipitated seizures of angina pectoris. Extensive subendocardial myocardial necrosis of left ventricle at autopsy.

A. (Top) Electrocardiograms during the bouts of bleeding disclosed RS-T depressions and T-wave inversions in Leads I and II. During the second hemorrhage the T wave in Lead III and, during the third attack, in Lead IV, was, in addition, transiently inverted. The final episode of hemorrhage produced a supraventricular tachycardia, marked depressions of RS-T segment in Leads I, II, and IV and large Q wave in Lead III.

B. (Bottom) Photomicrograph of section from left ventricle. Subendocardial layer revealed disseminated focal and often confluent areas of acute myonecrosis. Occasionally a thin strip of uninvolved muscle was present immediately beneath the endocardium, interposed between the intact endocardium and the involved muscle. Homogenization, loss of striation, tinctorial changes, loss of nuclei, profound necrosis of muscle fibers, scattered hemorrhages and reactive cellular infiltration were observed.

dilated, as occasionally occurs despite the presence of arteriosclerotic plaques.[15]

Histologic changes were pronounced in scattered portions. The involved areas were focal and limited to the papillary muscles and subendocardial region of the posterior wall of the left ventricle. These consisted of tinctorial alterations, loss of striation, hemogenization and necrosis of myocardial fibers, together with a reactive infiltration composed principally of polymorphonuclear leukocytes.

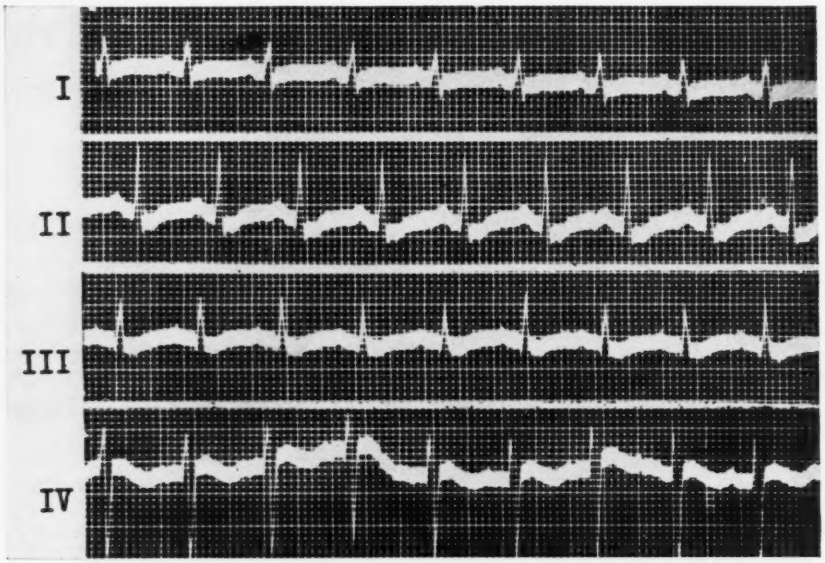

FIG. 5.—T. L., a 19 year old woman with ulcerative colitis and intestinal bleeding. Following massive hemorrhage, death occurred. The heart was not enlarged; the coronary arteries were normal; there was focal, acute myonecrosis of anterior and posterior walls and papillary muscles of left ventricle. The electrocardiogram disclosed depression of RS-T segment in Leads I, II, and III and low T waves in all leads.

The anatomic diagnoses were: acute, focal, subendocardial myonecrosis of posterior wall and papillary muscles of the left ventricle; focal myofibrosis; coronary arteriosclerosis without narrowing; inactive, moderate rheumatic valvulitis of the mitral, aortic and tricuspid valves.

Comment: Although the clinical picture during periods of severe gastrointestinal hemorrhage suggested acute coronary artery occlusion, the electrocardiograms were considered characteristic of acute coronary insufficiency. This impression was confirmed at autopsy by the presence of microscopic areas of focal, acute myonecrosis in the absence of acute coronary occlusion. Coronary arteriosclerosis and rheumatic valvular disease were predisposing factors to coronary insufficiency while severe bleeding, hypotension and shock constituted the precipitating mechanisms.

Case 5.—T. L., a 19 year old housewife with moderate rectal bleeding for two months due to ulcerative colitis, had had fever of 101 to 105 F. for three weeks, and a spontaneous miscarriage with moderate uterine hemorrhage one week prior to admission. She was disoriented, semistuporous and pale. The pulse rate was 128; respiratory rate varied from 30 to 40. The systolic blood pressure was 130; the diastolic could not be determined. The heart was not enlarged, the sounds were forceful, the rhythm regular; an apical presystolic gallop and a precordial systolic murmur were audible. Bilateral basal pulmonary râles were heard. The hemoglobin was 14 per cent, red blood cell count 885,000 per cu. mm., and leukocyte count 23,700 per cu. mm. of which 69 per cent were neutrophiles. The electrocardiogram (fig. 5) showed a depressed RS-T segment in Leads I, II and III and flattened T waves in all leads. The patient improved slowly following transfusions; the hemoglobin rose to 32 per cent. However, one week after admission she suddenly passed numerous tarry stools and succumbed.

At autopsy, the heart weighed 225 grams. Beneath the endocardium of the trabeculae carneae and within the papillary muscles of the left ventricle were pale yellow streaks, while on section scattered areas of the musculature showed similar involvement. Microscopically, minute disseminated areas of ischemic change were noted within the subendocardial layers of the anterior and posterior walls of the left ventricle and within the papillary muscles. These were focal, pin-point areas of myocardial degeneration consisting of disappearance of nuclei, obscuration of myofibril outlines, foci of hemorrhage, necrosis and reactive acute and subacute inflammation.

Comment: Massive intestinal hemorrhage in a 19 year old girl suffering from anemia secondary to ulcerative colitis, resulted in focal myonecrosis in the wall of the left ventricle in the presence of normal coronary arteries and an otherwise normal heart.

Physiologic and Biochemical Considerations

It is pertinent to consider briefly the physiologic effects of hemorrhage upon the coronary circulation. Moderate blood loss causes a diminution in cardiac output, arterial blood pressure, circulating blood volume and venous return to the heart. These constitute the initiating factors in the vascular readjustments following acute hemorrhage.[16–24] These alterations effect the vasopressor reflex, which in turn produces compensatory peripheral vasoconstriction, accelerates heart rate and tends to return blood pressure to normal. It is significant, however, that following the initial stage of reduced cardiac output and lowered blood pressure, a compensatory increase in cardiac output often occurs despite a decreased blood volume.[25] This mechanism helps deliver a normal oxygen supply to the peripheral tissues by increasing circulation rate and oxygen utilization. It has been well established on clinical and experimental grounds that uncomplicated, severe hemorrhage may also produce a state of shock similar to that due to other causes.[17, 19, 26–28]

Vasoconstriction generally is beneficial, helps maintain blood pressure and effect an adequate blood flow to vital organs.[22, 29, 30] The question whether the coronary arteries participate in the generalized reflex vasoconstriction is of clinical importance. To such a possibility has been ascribed the development of acute coronary insufficiency as evidenced by electrocardiographic abnormalities, particularly following hemorrhage from the gastrointestinal tract.[31, 32] However, conclusive proof of such effect has not been adduced experimentally.

In continued bleeding all compensatory readjustments ultimately fail, the cardiac output is reduced strikingly with resultant irreparable damage to the cerebral vasomotor centers and cardiac muscle, and irreversible shock supervenes.

That the state of the myocardium contributes significantly to recovery from shock has been re-emphasized by Wiggers[33–35] who has suggested that myocardial impairment rather than peripheral circulatory failure was responsible for the state of irreversible shock following hemorrhage. Lawson and Rehm[36] have shown that when hemodilution has occurred in the terminal phases of post-hemorrhagic shock, the blood volume and venous pressure may be increased and the heart dilated, denoting myocardial damage and failure. Kohlstaedt and Page[20] considered that cardiac dilatation is the critical point at which irreversible changes appear following hemorrhage, for up to this point infusion was therapeutically successful in their animals. In view of these observations, it would appear that the heart muscle is particularly susceptible to change in the presence of hemorrhagic shock and, in turn, exerts considerable influence in recovery.

An important consideration in a study of the effect of hemorrhage on the circulation is the quantity and rapidity of blood loss. It has been demonstrated that in the normal, average-sized man no serious effects appear if the hemorrhage is less than 30 per cent of the blood volume or less than 3 per cent of the body weight, i.e., less than 1,500 cc. of blood.[18, 22, 23, 37] On the other hand, in patients with organic heart disease, pulmonary disease, chronic anemia, etc., a loss of even 500 cc. of blood is tolerated poorly. The amount of blood loss, furthermore, has been related to electrocardiographic changes. Thus, Scherf and Klotz[32] found no electrocardiographic abnormalities in two normal persons from whom 850 cc. and 400 cc. of blood, respectively, had been withdrawn. However, loss of even smaller quantities of blood proved to be

very significant in the presence of coronary artery disease or other factors predisposing to coronary insufficiency.

The rapidity of the fall may be of greater significance than the actual decrease in hemoglobin. In patients with chronic anemia who remain at rest, for example, the hemoglobin may fall to very low levels without producing evidences of coronary insufficiency. The compensatory mechanisms usually suffice to maintain normal coronary blood flow at rest. In active hemorrhage, on the other hand, if the hemoglobin concentration rapidly decreases 20 per cent or more, acute electrocardiographic changes frequently appear and occasionally anatomic myocardial alterations occur.

Biochemical studies following hemorrhage have yielded evidence of marked disturbances in tissue metabolism, involving electrolyte patterns and acid-base balance, with deleterious effects upon the coronary circulation and myocardium.[19, 38–42] In posthemorrhage shock there is also a striking reduction in tissue oxygen consumption, a mechanism which may be as important a cause of tissue anoxia as the reduced blood flow.[43]

Clinical Observations of Coronary Insufficiency and Myocardial Involvement following Hemorrhage

As long ago as 1842, Hall[44] wrote: "Hemorrhage not only induces syncope, but occasionally sudden death, due to interruption of the coronary blood supply. . . . Impaired coronary circulation may arise from impeded flow of blood through arteries contracted by ossification, or impeded by adipose substances. . .or from an insufficient condition of blood itself in cases of hemorrhage and anemia."

The significance of the relationship between hemorrhage and cardiac sequelae, first suggested by Hall, was not generally recognized until the 1930's, when Dietrich and Schwiegk,[1] Büchner,[5] and Goldenberg and Rothberger[45] showed that anoxemia constituted an important precipitating cause of acute coronary insufficiency. Hicks[46] later demonstrated that cardiac muscle, unlike skeletal muscle, is unable to go into temporary oxygen debt when the coronary circulation is impaired. Since that time the importance of cardiac muscle damage following blood loss has been emphasized repeatedly by investigators abroad and in this country.[1, 3–8, 13] Friedberg and Horn[6] found hemorrhage to be responsible for myocardial necrosis in 2 of their 34 cases of myocardial infarction without coronary artery occlusion and offered the opinion that the factor of shock was most important. Master, Jaffe and Dack[47] described an instance of extensive myocardial infarction following severe gastrointestinal hemorrhage. Similar experiences were reported by Bean,[48] Gross and Sternberg,[7] McLaughlin, Baker and Sharpe,[49] and Master, Gubner, Dack and Jaffe.[9] On the basis of these and his own observations, Master[50] emphasized the importance of hemorrhage as a cardiac emergency and urged early and repeated transfusions to forestall the development of coronary insufficiency. Additional clinical reports have appeared more recently.[51–57]

The belief that hemorrhage exerts an important deleterious effect upon the myocardium is fortified by the clinical observations that heart failure either may be induced or worsened by hemorrhage.[9, 13, 47, 57] Heart failure was precipitated in 10 per cent of the cases included in this report. These observations emphasize the fact that hemorrhage is dangerous in patients with heart disease, and is of especially serious omen in those already in cardiac failure. Here both the cardiac failure and hemorrhage demand energetic treatment.

Electrocardiographic Considerations

The Electrocardiogram and Experimentally Induced Coronary Insufficiency. A number of observers[3–5, 58–62] have reported that, following severe or repeated bleeding of normal dogs and rabbits, flattening and inversion of the T waves and depression of the RS-T segments appeared. Tachycardia often developed. These changes were found similar to those observed in man during an attack of angina pectoris and in induced anoxemia.[1, 58, 59, 62] Presumably both diminished coronary flow and anoxemia might be responsible for the abnormal electrocardiogram following experimental bleeding in animals.

Electrocardiographic Changes due to Subendo-

cardial Involvement. In acute coronary insufficiency due to any cause, proof has been established of the relationship of the characteristic electrocardiographic changes, i.e., RS-T depressions and T-wave inversions, to localization of the myocardial necrosis within the subendocardium and papillary muscles.[2, 3, 9, 31, 32, 63–72] Pruitt, Barnes and Essex,[71] and Pruitt and Valencia[72] described RS-T depression associated with experimentally produced lesions in the subendocardium of animals. Scherf and his colleagues[31, 32] reported transient T-wave and RS-T changes in cases of profuse gastric hemorrhage, which they attributed to reflex coronary artery spasm. The occurrence of focal necrosis limited to the subendocardium and papillary muscle was postulated since the electrocardiographic patterns resembled those produced by experimental injury to the inner surface of the heart.[64] These investigators observed that the more acute the loss of blood, the more marked were the electrocardiographic changes. It was their belief, moreover, that the electrocardiographic changes after acute hemorrhage were limited usually to the T wave and that only in severe cases did depression of the RS-T segment occur. They showed, further, that RS-T segment depression is regularly observed when anoxemia of the myocardium is widespread. Oerning, Sommerfelt and Fredriksen[73] described T-wave changes and RS-T depressions in more than one-third of their 74 patients in whom hemorrhage had occurred and thought that the electrocardiographic alterations were due to vasomotor reflexes affecting the coronary circulation and the myocardial anoxemia which followed. Our studies confirm the belief that the abnormal electrocardiographic pattern is due, primarily, to the involvement of the subendocardial region of the left ventricle.

The electrocardiogram may afford sensitive and objective evidence of coronary insufficiency. Alterations in the T wave appear readily following blood loss in bed patients, and it appears that especially when RS-T depressions co-exist, the presence of acute coronary insufficiency is to be assumed whether or not clinical signs have been detected. We have observed patients showing RS-T segment depressions who gave no other indication of cardiac impairment and, yet, in whom an unusual physical effort induced myocardial collapse.

Additional details of our electrocardiographic findings will be reported subsequently. However, one observation seems worthy of comment here. Although T-wave inversion and depression of the RS-T segment are characteristic of the electrocardiogram following hemorrhage, as in other forms of acute coronary insufficiency, in 3 instances a deep Q wave ultimately appeared. These patients died. Permission for an autopsy examination was obtained in one case only (Case 3); widespread subendocardial necrosis was found in the absence of a recent artery occlusion. On the basis of this and other experiences, it is reasonable to assume that the coronary circulation had been reduced to such a degree previously that widespread myocardial necrosis followed the massive hemorrhage, and was responsible for the appearance of large Q waves in the electrocardiogram. In bleeding patients, the development of large Q waves in a tracing hitherto distinguished only by the presence of RS-T depression and T-wave inversions may signify extensive myocardial necrosis and antecedent heart disease.

Active therapeutic measures are indicated as soon as T-wave or RS-T segment alterations appear in the electrocardiogram. In our opinion a progressive decrease in amplitude of the T wave is sufficient proof that the loss of blood has produced a harmful effect upon the myocardium.

Therapy

The treatment for hemorrhage is, of course, adequate blood transfusion. Whole blood should be given especially early to those patients in whom a predisposing factor of coronary insufficiency is suspected. Coronary arteriosclerosis, valvular disease, hyperthyroidism, congestive heart failure, and chronic anemia are factors which predispose to the occurrence of acute coronary insufficiency and constitute dangerous potentialities.

Treatment should be instituted before the myocardium is impaired, since in such state intravenous infusion will be to little or no avail.[20, 33, 34, 50, 62] The value of the daily electrocardiogram lies in the fact that not only

is it an objective sign of coronary insufficiency but also that it will reveal RS-T depressions and T-wave inversions which may precede the appearance of clinical evidence of coronary insufficiency. Blood should be administered until bleeding has ceased and pulse rate, blood pressures, hemoglobin determinations and electrocardiograms have been restored to normal values.

The treatment of the angina pectoris which appears during hemorrhage is blood replacement.[74–76] The occurrence of chest pain or the aggravation of pain ordinarily experienced by the patient constitutes an urgent indication for therapy. It is significant that chest pain had appeared in 18 of our patients and in each instance blood transfusion effected either amelioration or disappearance of this complaint. The advisability of repeated transfusions may be questioned in patients with organic heart disease, in view of the possibility of inducing left ventricular failure. Such eventuality is readily admitted. However, we firmly believe that the occurrence of this complication can be prevented, or its severity minimized, even when frequently repeated transfusions are indicated, by careful and slow administration of blood. Constant and studied clinical supervision is imperative.

Summary

1. Hemorrhage is one of the most frequent and important precipitating causes of acute coronary insufficiency and assumes grave significance in patients whose coronary circulation is already imparied by antecedent heart disease such as coronary arteriosclerosis, aortic stenosis, enlarged heart. In such patients acute hemorrhage may be followed by myocardial ischemia of sufficient severity and duration to produce clinical, electrocardiographic and anatomic evidence of acute coronary insufficiency.

2. A review has been presented of 103 cases of acute, moderate and severe hemorrhage with references to the amount of rapidity of hemorrhage, blood hemoglobin level, heart rate, blood pressure, presence of shock and electrocardiographic changes. The gastrointestinal tract was the source of bleeding in 95 cases. Fifty-nine cases (57 per cent) presented clinical or electrocardiographic evidence of acute coronary insufficiency; of these, 32 showed electrocardiographic changes alone, 6 only clinical findings and 21 had both clinical and electrocardiographic evidence. The age of patients who developed coronary insufficiency ranged from 18 to 79 years.

3. Twenty-two patients succumbed to the effects of hemorrhage; 18 of these presented clinical or electrocardiographic features of acute coronary insufficiency. In 4 of 13 autopsied cases, pathologic examination disclosed subendocardial myocardial necrosis in the absence of recent coronary artery occlusion.

4. Of the 27 patients with clinical evidence of coronary insufficiency, substernal or precordial pain occurred in 15 instances, congestive heart failure in 8, and both together in 3. Precordial pain varied from mild to severe in nature. In 6 instances its association with shock, tachycardia, and fall in blood pressure simulated massive myocardial infarction due to acute coronary artery occlusion. These symptoms and signs were transient and responded rapidly to therapy. This was especially striking in several cases of recurrent hemorrhage in which each bout of hemorrhage precipitated an episode of severe angina pectoris.

5. Significant electrocardiographic changes occurred in 53 patients. These consisted of flat or inverted T waves in 24 instances, RS-T depression in 4 cases, and combined RS-T and T changes in 25 cases. The latter findings represented the severest degree of coronary insufficiency. Although alterations occurred in all leads, Leads I, II and IV were most frequently affected. Reduced coronary blood flow resulting in anoxia, particularly of the subendocardium, was responsible for the RS-T depressions and T-wave inversions.

6. The changes in circulatory dynamics which were found to be associated with coronary insufficiency following hemorrhage include the shock state, tachycardia, drop in blood pressure and decreased blood volume. Although anoxemia due to fall in hemoglobin was important, it was observed that coronary insufficiency occurred in the absence of anemia when the clinical features of shock predomi-

nated. This emphasizes that rapidity of blood loss may be more significant than the actual amount.

7. The morphologic myocardial changes, when present, varied from tinctorial changes, smudginess of myofibrils and focal necrosis to grossly recognizable confluent zones of infarction. The ischemic lesions were usually noted in the subendocardial region of the posterior wall, septum and papillary muscles of the left ventricle. Pericarditis and mural thrombosis were conspicuously absent. Although coronary arteriosclerosis and varying degrees of stenosis of the lumen were often present, acute coronary occlusion was not found.

8. Hemorrhage exerts a deleterious effect upon the myocardium and was responsible for the production of heart failure in 10 per cent of the cases herein reported. By the same mechanism, hemorrhage may intensify the cardiac failure already present.

9. The proper therapy of shock and anemia following acute hemorrhage in essential for prophylaxis and therapy of coronary insufficiency. Blood should be administered promptly and adequately, particularly in patients with predisposing factors of coronary insufficiency.

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Delayed Development of Ventricular Ectopic Rhythms following Experimental Coronary Occlusion

By A. Sidney Harris, Ph.D.

Following aseptic occlusion of the anterior descending artery of the dog's heart ectopic ventricular tachycardia develops after a latency of four and one-half to eight hours, and persists for two to four days. Large gross infarcts are found in all hearts. The duration of latency of onset of major ectopic activity approximates the minimal period of ischemia required to produce histologic signs of necrosis. It is suspected that products or processes of necrosis have excitatory effects on tissues bounding the ischemic zone. Evidences concerning various possible excitatory factors are briefly reviewed.

PREVIOUS experimental studies on ventricular ectopic activity following coronary occlusion, with few exceptions,[1, 2] have been confined to observations made within a brief acute period after occlusion, though both experimental[1, 2] and clinical[3, 4, 5, 6] reports have shown that ventricular arrhythmias may develop after periods of many hours and even days after obstruction of the artery. The scarcity of experimental studies upon the delayed development of ventricular arrhythmias and fibrillation perhaps is attributable in part to the high rate of early mortality[7, 8, 9] via ventricular fibrillation, which results from abrupt occlusion of one of the two major rami of the left coronary artery, and perhaps in part to the observation that in hearts that survive the first few minutes, ectopic activity ceases or nearly ceases[10] within ten to twenty minutes, and observations were terminated because continuation seemed useless.

In experiments preliminary to this study a method was discovered whereby the loss of animals by ventricular fibrillation during the immediate period of danger could be prevented in all cases. Ectopic activity which arose later could then be recorded and analyzed without the obstacle of high early mortality. This study is devoted to recording and analysis of the *delayed* ectopic ventricular activity following coronary occlusion.

The *early* development of ectopic ventricular discharges and ventricular fibrillation which often follows the experimental abrupt occlusion of a large coronary artery in the dog has been analyzed in some detail in previous reports.[8, 10] It was observed that the period of susceptibility to early ventricular fibrillation was brief, and that each fibrillation was initiated by a paroxysm of ventricular ectopic systoles accelerating in frequency. Fibrillation did not occur later than the tenth minute of occlusion though in some of the nonfibrillating trials the occlusion was maintained for thirty minutes before release of the artery. The frequency of ventricular premature systoles was at its maxium during the period from about the fifth to the eighth minute, after which it slowly declined. In some trials the ventricular premature systoles ceased entirely after ten to twenty minutes, and in others the ectopic frequency continued at a slow rate of about 1 to 5 per minute.

A causal relationship between ventricular premature systoles and the initiation of ventricular fibrillation has been demonstrated and the mechanism explained in a series of papers.[8, 10, 11, 12] The problem of the genesis of ventricular fibrillation, in a fundamental sense, contains the problem of ventricular ectopic discharges.

Procedures

Male dogs weighing 10 to 22 Kg. were used in all experiments. In the first series of animals, morphine (about 2 mg. per Kg.) and the minimal dose of barbital sodium necessary for surgery (180 mg. per Kg. intravenously) were used. If extra morphine was needed after awakening, it was given. Pentothal sodium and pentobarbital sodium have been used

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in later experiments for comparison of possible effects of changed duration of anesthesia upon the time of development of delayed ectopic activity.

During the preliminary acute experiments the chest was opened by a midline incision of the sternum. The anterior descending artery was dissected free for a few millimeters near the distal edge of the left auricular appendage and ligated there. After three of the first four hearts developed ventricular fibrillation within a few minutes of ligation, two-stage occlusion was tried. A double ligature of sufficient length was passed under the freed artery by a small curved forceps or a small aneurysm needle. The double ligature was cut, thus becoming two ligatures. The first ligature was drawn snugly but not tightly around the artery together with a 20-gage hypodermic needle. The needle was withdrawn immediately, leaving the artery constricted but still permitting some blood to pass. The second ligature was tightened one hour after the first in early experiments. Later the waiting period was shortened to thirty minutes. The second ligature completely and permanently closed the artery.

This method was successful to such a degree that its use in three open chest experiments and in *more than 60 aseptic occlusions* through a small opening in the thoracic wall has produced only one early ventricular fibrillation. In that one case the first ligature was too tight. It indented the arterial walls so deeply that the lumen remained occluded after the needle was removed. Only a few ventricular premature systoles have been seen following partial occlusion in any other experiment after the first ligature, or in the first few minutes following the subsequent total occlusion.

After the procedure of two-stage occlusion was developed, aseptic methods were employed in all operations. The ligatures were applied through a small opening in the fourth interspace. The wounds were closed in layers and the animals were kept for periods varying up to forty-six days, though almost all of them were sacrificed or died within two weeks after the operation.

Results

Following the tightening of the second ligature, i.e., the completion of the occlusion, electrocardiograms were made at frequent intervals, and observations of the electrocardiographic deflections for movements indicative of ventricular ectopic beats which might not be included in brief records were made even more frequently and often continued for many minutes at a time.

The records in figure 1 illustrate the electrocardiographic (Lead II) findings during the development of ectopic activity. The control record was made shortly after the administration of the anesthetic. The animal was asleep, but not fully anesthetized. The record shows normal complexes, a relatively slow rate, a normal sinus arrhythmia. Four hours and thirty minutes after occlusion, the rate was faster but there were no premature ventricular beats. At five hours and twenty minutes complexes of ectopic ventricular origin had begun, and at times were fairly numerous, though their rate was not yet rapid. After eight hours the ectopic activity was dominant. It was difficult to find a normally initiated beat in long strips of record. None are contained in the piece shown. The discharges were multifocal. The rate was about 160 per minute. In some other experiments the maximal ectopic rate has been as high as 250 per minute.

A chart to illustrate more quantitatively and over a longer time the rate of development and subsidence of ventricular ectopic activity in an experiment in which morphine–barbital sodium anesthesia was employed is reproduced in figure 2. This is a plot of data from the first animal of the aseptic series. During the first four hours following occlusion there were occasional ectopic ventricular beats. Sometimes there were 1 to 3 per minute. At other times there were none during many minutes of observation.

Between the ends of the fourth and sixth hours, the ectopic ventricular frequency increased sharply. By the end of the eighth hour all beats were of idioventricular origin. This completely ectopic ventricular rhythm continued from about the eighth hour of occlusion until sometime between the fifty-first and sixty-ninth hours. During the third postoperative day ventricular ectopic beats persisted at a frequency of about one-half the total heart rate. No ectopic beats were observed on the fourth day. The maximal frequency of the abnormal complexes in this experiment (250 per minute) was recorded at twenty-one hours. There was a slight diminution to 230 at thirty hours and to 160 on the second day (forty-eight hours). This general pattern of rise and decline was found to be characteristic of the series, but with the time of beginning of the rapid rise in frequency of ectopic complexes

varying in a large majority of experiments between four and one-half and eight hours, and the duration of ectopic activity varying between two and five days.

The maximal rate of ectopic activity was reached in all experiments by the thirtieth hour. In the usual case it was reached within ten to twenty hours, and persisted at a high level throughout the first postoperative day.

During the period of occasional or developing ectopic activity, it was necessary to observe the electrocardiographic deflections for minutes at a time and to count in order to make accurate estimates. During the early part of the delayed rise there were periods of three or four minutes when no ectopic beats were seen. Then two or three might appear in succession or within a few seconds. Even with ectopic beats averaging 30 to 40 per minute, as many as 10 or 15 consecutive normally initiated complexes sometimes were observed. Interspersed with such successions were periods when almost all beats were from ventricular pacemakers. It appeared that a ventricular focus (often more than one) with a frequency of impulse formation almost equal to that of the S-A node was

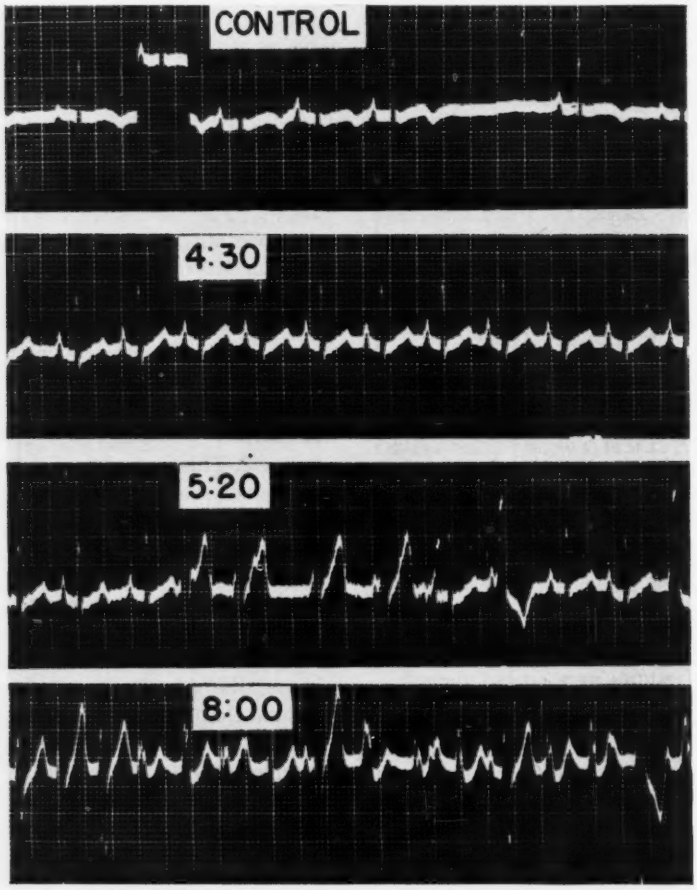

FIG. 1.—Electrocardiograms illustrating development of ventricular ectopic activity following coronary occlusion. Control record was made with dog under morphine–Pentothal sodium anesthesia before operation. Other records were made four hours thirty minutes, five hours twenty minutes, and eight hours after total occlusion.

alternately gaining and losing dominance of the cardiac rhythm. Such interplay between the S-A node and subordinate pacemakers has been well described.[13]

With further increase in ectopic activity normal complexes became fewer and eventually were completely or almost completely supplanted by ectopic forms. At the height of ectopic activity the rate of the idioventricular discharges usually did not vary greatly. Only exceptional experiments showed significant variations in ectopic activity on the first post-

barbital anesthesia might be a governing factor. A series of operations were then performed using Pentothal sodium, pentobarbital sodium, and ether anesthesia. Ether was used in the smallest number of experiments, four. The animals awoke from each of these anesthetics more rapidly than from morphine and barbital. The animals given Pentothal sodium were quite active within two to three hours after the completion of the operation. When they moved themselves about vigorously on their hammocks, showing excitement in their partly nar-

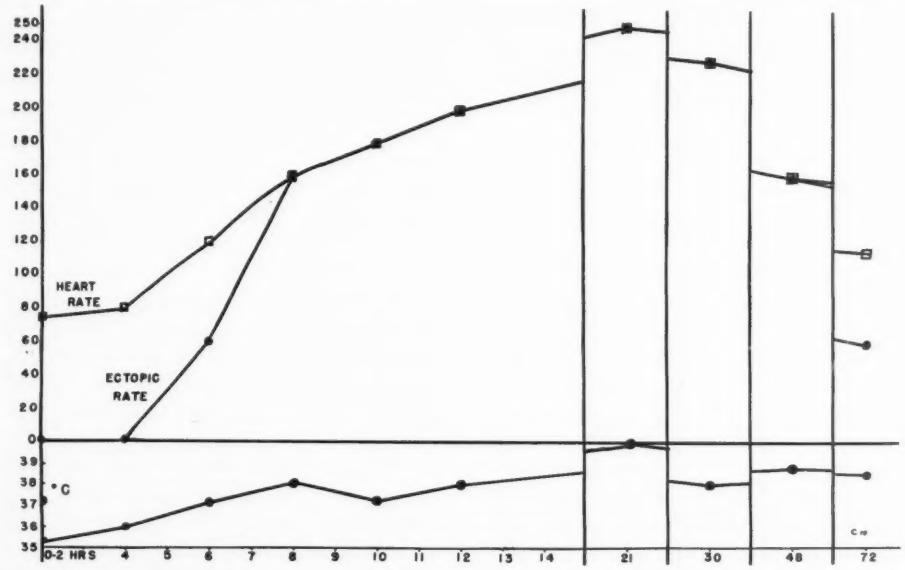

FIG. 2.—Chart showing heart rate (normal beats plus ventricular premature systoles) and frequency of premature beats as they changed with time after occlusion of the artery. Lower curve, rectal temperature. Operation performed under morphine–barbital sodium anesthesia.

operative day when the excitatory drive (of whatever kind) of the ectopic pacemakers was most intense.

During the subsidence of ectopic activity on later days alternating periods of dominance by the normal and ectopic pacemakers apparently similar to those seen during the time of development of ectopic discharges reappeared.

Relation to the Anesthetic. The consistent repetition of the four and one-half to eight hour latency before the onset of the rapid rise of activity in ventricular foci led to a suspicion that the lessening of effect of the morphine–

cotized state, some of them exhibited premature systoles which ceased spontaneously or became greatly diminished when the animal became calm. Sedation by morphine or a small dose of pentobarbital sodium or barbital sodium was effective in quieting the animal and causing the ectopic discharges to cease for a time. After four and one-half to five hours, however, sedation and sleep no longer were effective in preventing or stopping ectopic activity, though doses of pentobarbital sodium, 15 mg. per Kg., and barbital sodium, 60 mg. per Kg., were tried in different experiments.

The animals operated under ether exhibited no significant increase in early ectopic activity over that of the first four and one-half hours following occlusion under morphine and barbital sodium. Following pentobarbital sodium there were moderate increases between three and four and one-half hours after occlusion, but as in the Pentothal sodium experiments they were easily controlled until the main rise made its appearance, after which half anesthetic doses of pentobarbital and the resulting deep sleep made no observable change in the steep rise in ectopic frequency.

The evidence indicates that the usual latent period of four and one-half to eight hours between occlusion and the onset of the steep rise of ectopic activity is not due to the time required for awakening from anesthesia.

Relation to Temperature Changes. The charts almost consistently show a rising rectal temperature during the period of increasing ectopic activity. In two experiments, however, the main increase in temperature occurred during the two hours just preceding the detection of any rise of ectopic activity. In three experiments the temperature showed a downward fluctuation while the ectopic frequency was rising. On the second or third postoperative day it was not uncommon to find ectopic activity subsiding while the temperature held a level near its maximum. In many experiments there was a striking parallelism between temperature and ectopic frequency. It is possible that both are related to tissue changes that resulted from ischemia of the myocardium. In some experiments the temperatures fell postoperatively to levels significantly below the control readings of 37 to 38° C. Recovery from the low temperature in these experiments fused with the rise which occurred after a few hours in all experiments. The presence or absence of an initial fall in temperature bore no consistent relation to the maximum temperature eventually reached, nor to the intensity of ectopic activity attained. The highest temperature observed was 40.2° C. The delayed rise in ectopic ventricular activity is independent of the rise in temperature, though they sometimes follow parallel courses. It is probable that there are common predisposing factors.

Level of Occlusion. The distances of the ligatures from the ostia of the left coronary arteries were measured in all of the first 36 hearts of the aseptic series after preservation in formalin. These distances, together with associated mortality rates (seventy-two hours) and the number and percentage of animals in the different ligature-distance groups that developed rapid ventricular tachycardia within the usual time range are summarized in table 1.

Of a total of 10 animals in the group with ligatures nearest the ostia, 4 died during drug tests and therefore are excluded from the mortality table. Of the remaining 6, 5 died at periods varying from two hours fifty-five minutes to seventeen hours after ligation. Only one of these 5 animals that died developed more than an occasional ectopic beat at any time. All were very weak and dyspneic. It is probable that all of them died of myocardial failure leading eventually to cessation of pacemaker action. The 4 animals that were killed in drug tests had developed rapid ventricular ectopic rhythms and did not appear so weak as did the previously described group. Throughout the study it was observed that the animals that appeared very weak and ill usually produced few ectopic discharges, though there were exceptions.

In the 30 animals with ligatures between 1.5 and 3.0 cm. from the ostia, the mortality rates ranged from 25 to 33 per cent in the various subdivisions. The percentage of animals that developed rapid ectopic ventricular tachycardia was significantly higher in those hearts with the ligatures 2 to 3 cm. from the ostia than in those with more proximal ligatures. Ligatures placed within this distance range offer the highest probability of yielding surviving animals with rapid ectopic discharges for purposes of investigations upon this phenomenon. As a surgical guide ligatures should be placed 5 to 8 mm. distal to the edge of the left auricular appendage.

Infarction. No animals were sacrificed earlier than six days after operation, though some died earlier. A report on the first 25 dogs of the series will fairly present the gross observations on infarction. Twenty-one of these dogs were sacrificed at periods varying from six to twenty-five

days after the occlusion. Two others died at eighteen and one-half and twenty hours following occlusion after developing ectopic ventricular tachycardia in the typical manner. One died two hours and another three hours after occlusion. Gross infarcts with approximately normal thickness of the wall were clearly apparent in 16 of the 21 hearts that survived long enough to produce them. The infarcted muscle was stiffened in some hearts, and in others it was very soft, approaching liquefaction. The epicardial surface of the infarcted area of some hearts was rough.

The line of demarcation between necrotic and normal myocardium usually was very sharp. This was particularly true upon viewing the endocardial surface and cuts across the boundary region within the muscle.

TABLE 1.—*Relation of Early Mortality (72 Hours) and of Development of Ectopic Discharges to Distance of Ligature from Ostium of Left Coronary Artery.*

Distance of Ligature	No. of Animals	Mortality in 72 Hours		Rapid Ectopic Systoles	
		No.	%	No. of Animals	%
Cm.					
1.1–1.5	6*	5	83	2 (6 of 10)*	33 (60)*
1.6–2.0	15	5	33	9	60
2.1–2.5	11	3	27	9 (10 of 12)*	82 (83)*
2.6–3.0	4	1	25	4	100

* Animals that were killed in the process of drug testing during the first 72 hours could not be included in the mortality table. There were 4 such animals in the 1.1–1.5 cm. group and 1 in the 2.1–2.5 cm. group. The inclusion of these animals in the data on development of rapid ventricular ectopic systoles produced the figures given in parentheses.

The other five hearts of dogs that were sacrificed after a period sufficiently long to produce infarction were found to have greatly thinned anterior left ventricular walls (to about 2 mm.) and the color of the remaining tissue in this area was a paler more grayish-yellow color than the muscle of other areas. Usually it was very tough and fibrous, though the epicardial surface bore the appearance of muscle. It was evident that much tissue had been removed from these thinned walls, and that, like the hearts with obvious thick infarcts, the anterior wall of the left ventricle had suffered severe necrosis. In these five it appeared that the outer layer of muscle had survived and that fibrous tissue had been added, leaving a thin but strong tough scar. In these hearts the durations of occlusion were 11, 12, 14, 20 and 21 days. In some of the other hearts with similar durations of occlusion (one twenty-five days) the infarcts were hard, not thinned, and were without evidence of processes of softening or dissolution. In these, and in other hearts with infarcts undergoing liquefaction, the necrosis often extended through the entire wall except a very thin, not easily detected, endocardial layer. Liquefaction and canalization extended almost through the walls of two hearts, but there were no ruptures.

Microscopic studies of tissues from the ischemic or infarcted areas have been made from hearts of animals that survived coronary occlusion for periods varying from two hours to twenty-five days. The findings were similar to those reported by others.[14, 15, 16]

Tissues from ischemic areas of hearts of animals that died two and three hours after occlusion appeared normal on microscopic examination. Definite changes were seen in sections from animals that died six hours thirty-five minutes, nine hours forty minutes and ten hours after occlusion. Among the changes observed in these specimens were leukostasis, leukocytic infiltration, hyaline changes in the muscle fibers, fragmentation of muscle, changes in staining properties, vacuolation and changes in the nuclei.* Mallory and co-workers have reported that histological evidence of necrosis can be detected within five or six hours after occlusion.[15]

Discussion

The discovery that by two-stage occlusion the immediate loss of animals by ventricular fibrillation could be circumvented has been of the greatest value in facilitating the study of delayed ectopic ventricular activity. The reason why protection against immediate ventricular ectopic rhythms and ventricular fibril-

* Dr. Berne L. Newton of the Baylor University Department of Pathology kindly examined the stained sections of specimens from the infarcted muscle and gave descriptions of his findings.

lation (first ten minutes) results from partial occlusion for thirty minutes before total occlusion has not been determined. Others[17] who have cited a preliminary report on this finding[18] have assumed that the protection results from the development of collateral circulation during the partial occlusion period. It should be remembered however that extensive and severe myocardial necrosis develops in each of these hearts. This seems to be a strong argument against an important development of collateral circulation within so brief a period. Others have reported from experimental observations that a longer period is required to develop a measurable increase in collateral circulation.[19] It is probable that during the thirty minutes of partial occlusion accommodation of the muscle fibers to the kind of excitatory influence that causes the early ectopic activity develops. A few hours later other kinds of excitatory factors apparently arise.

Site of Origin of Ectopic Impulses. Evidence from earlier studies on excitability changes in moderate and severe anoxia in heart muscle[20] and from local lead recording of time of activation in different regions of the ventricular surfaces during coronary occlusion[10] indicates that ectopic discharges that arise within a few minutes after sudden occlusion originate in the partially ischemic boundary between the fully ischemic and normally circulated areas of muscle. Observations in chronic experiments of severe necrosis in the region of infarction and of the entirely normal appearance of muscle outside of the infarct in animals sacrificed after five to twelve days indicate also, by elimination, that the boundary zone is the probable site of pacemakers in delayed ectopic activity. This boundary is extensive. It is made up of (1) a thin band of tissue forming a circumference around the fully ischemic area and extending in a majority of hearts from the epicardium to within a fraction of a millimeter of the endocardium; (2) a thin sheet of tissue between the ischemic muscle and the endocardial layer; and (3) in some hearts a thin sheet of tissue between the ischemic muscle and a spared external (epicardial) layer. The circumferential band is complicated in that the infarct extends onto the septum including the anterior third or fourth of it from the level of the ligature to a distal limit near the apex. The boundary, therefore, divides the septum. It also extends along the edge of the right ventricle.

The form of the electrocardiographic deflections during low frequency ectopic activity often indicates a predominant single focus. As the activity becomes more frequent, i.e., as the intensity of the ectopic excitatory drive becomes greater, the form of the complexes shows many variations indicating multifocal origins.

Factors in Ectopic Excitation. Moderately anoxic heart muscle has been shown to be hyperexcitable by measurement of its threshold to electric stimuli.[20] This hyperexcitability exists when the whole heart is subjected to the same degree of anoxia; therefore it cannot be attributed to an injury potential, though in regional ischemia the injury potential undoubtedly adds another factor of excitation (see next paragraph). Within a very thin sheet of boundary cells between ischemic and nonischemic muscle there is a transition from adequately circulated cells to cells that are ischemic to a degree sufficient to produce complete inactivation followed by necrosis. Within the transition sheet there are cells in all stages of ischemic hypoxia and anoxia; therefore some cells will be within the range that produces hyperexcitability. However, anoxia alone when produced slowly by rendering the whole animal anoxic does not cause ectopic impulses.[8] It may be inferred then that some other excitatory factor or factors must act upon these border cells made hyperexcitable by partial anoxia or ischemia to evoke discharges. Some of the possible additional factors are injury potentials, sympatho-adrenal stimulation, histamine, and possibly other excitatory products liberated from tissues.

Injury Potentials. From neurophysiology it is known that the region of nerve near an injury is hyperexcitable and that it may discharge impulses spontaneously[21] or respond to stimuli that would be subthreshold to a region of nerve farther from the injury.[22, 23] Hyperexcitability near an injured area of nerve extends 10 to 12 mm. from the injury, diminishing with distance.[22] This distance corresponds almost identically with the length of nerve adjacent to an

injury from which injury potentials of significant intensity have been recorded.[24] This hyperexcitability is attributable to the injury potential which produces a state of catelectrotonus and partial depolarization of the cell membranes within the region.[24]

An ischemic area of heart muscle becomes electrically negative with respect to the normally circulated muscle within about one and one-half minutes after obstruction of the artery.[25] The diastolic negativity of injured heart muscle is found in all parts of the injury and is said to have a sharp boundary coinciding with the boundary of the injured zone.[26, 27] Strong catelectrotonic effects of the injury potential undoubtedly exist in the boundary region. Injury potential, therefore, can be regarded as a probable contributing factor in ectopic ventricular excitation after coronary occlusion.

Sympatho-Adrenal Stimulation. Sympathetic impulses to the heart and injected epinephrine facilitate the production of ectopic ventricular beats.[28, 29, 30, 31, 32] Excision of the adrenal glands and stellate ganglia markedly reduced the ectopic activity and probability of ventricular fibrillation in experimental acute benzol poisoning in cats and monkeys.[33] The removal of the stellate and upper five thoracic ganglia has been reported to diminish markedly the occurrence of premature systoles, ventricular tachycardia and fibrillation immediately after sudden occlusion of a coronary artery.[34, 35] Many studies, recently reviewed by Raab[36] have shown that heart muscle contains high concentrations of epinephrine and epinephrine-like catechols.

All of these observations are consistent with the view that sympatho-adrenal excitation may be a factor which contributes to the production of ventricular ectopic rhythms following coronary occlusion.

Histamine is present in the tissues of the body in quantities which are toxic when liberated.[37] When added to fluid bathing non-rhythmic heart tissues, histamine has induced rhythmic activity.[38, 39] Cardiac muscle releases histamine-like substance continuously. The amount is increased by increasing the work of the heart, by anoxia and by increased carbon dioxide.[40] Blood histamine is increased by slow intravenous injection of epinephrine.[41] There is evidence that histamine, tyramine, and possibly other amino acid derivatives present in tissue extracts sensitize heart tissues to epinephrine.[42]

It appears possible, therefore, that in regional ischemia histamine and other products liberated from proteins in the ischemic muscle could diffuse to the hyperexcitable cells and there become factors in the discharging of ectopic impulses.

Correlation of Postulated Excitatory Factors to the Immediate, Intermediate and Delayed Phases of Ectopic Activity. There are three distinct periods which compose a time pattern in the manifestations of ventricular ectopic activity after experimental occlusion of a large coronary artery: (1) an *immediate* period of intense ectopic activity and danger of ventricular fibrillation within the first ten minutes, followed by (2) an *intermediate* period of little ectopic activity which lasts four and one-half to eight hours, and then (3) the *delayed* persistent period of intense ectopic drive begins.

The Immediate Period and Following Quiescent Hours. During the crescendo of ectopic beats that occurs within the first ten minutes after occlusion it is obvious that products of necrosis are not involved. Hyperexcitable partially anoxic boundary cells exist and they are subjected to the catelectrotonic effect of the injury potential which probably reaches its maximum by the end of one and one-half minutes[25] and continues. The increasing excitation which produces the rising ectopic frequency for the next few minutes occurs while the animal is under morphine-barbital or other barbiturate anesthesia of surgical depth; therefore it is unlikely that reflex excitation is responsible. It appears more probable that the direct effects of ischemia on the excitable membranes of the cardiac muscle cells produce this excitation and the subsidence which follows. Similar behavior of nerve receptors in ischemic skeletal muscle has been reported.[43]

Intermediate Period. During the quiescent period after the subsidence of action of the immediate period (or after the second ligature in two-stage occlusion) and before the delayed rise of ectopic activity, the ischemic-nonische-

mic boundary remains, and the injury potential has been found to be relatively constant at a high level in some recent experiments (as yet unpublished) during these hours. Evidently additional factors are required to produce rapid ectopic discharges, but for a number of hours these are weak or lacking.

Moderate increases in ectopic activity occurred in some animals during excitement periods while awakening from anesthesia, especially Pentothal sodium, two and one-half to four and one-half hours after the occlusion. These premature beats usually subsided when the animal became calm spontaneously and were controllable by sedation. This response to rest and to sedative drugs suggests that sympatho-adrenal excitatory factors may have produced the added excitation required for these moderately increased discharges during the hours prior to the main rise.

Delayed Ectopic Activity. Since the rapid rise of ectopic activity that begins four and one-half to eight hours after occlusion is not prevented nor visibly influenced by normal sleep nor by barbital sodium administered a short time before its beginning, it probably is determined by factors which are not dependent upon nerve impulses. The finding that the four and one-half to eight hour latency approximates the minimal period of ischemia found by pathologists to be necessary for the development of histologic evidence of necrosis may be more than fortuitous coincidence. It is of interest also that the circulation of a dog's limb must be obstructed for about six hours by tourniquet or ischemic compression in order to produce shock by this technic.[44] Recent experiments have indicated the presence of a vasoconstrictor substance with properties of norepinephrine in blood from dogs' limbs that had been ischemic for five hours.[45] It appears probable that processes and products of necrosis are of major significance in producing the intense delayed ectopic excitation that occurs during acute myocardial infarction in the dog's heart.

Possible Influence of a Delayed Increase in Collateral Circulation. In occlusions of the anterior descending artery in acute experiments the ectopic discharge frequency passed through a maximum and then subsided. The sudden release of the occlusion after the decline or cessation of ectopic beats caused a very brief return of high frequency ectopic discharges after about one minute. These quickly produced ventricular fibrillation in a high percentage of trials. In the few trials that did not terminate in fibrillation the rapid ectopic discharges lasted about ten seconds and subsided.

There is some evidence that the small collateral blood flow to the area made ischemic by the occlusion of the anterior descending artery remains relatively unchanged for a few hours and then begins to increase.[19] It has been suggested that the delayed increase of circulation could restore excitability in depressed cells, through a hyperexcitable stage similar in nature to that described on readmission of blood in the acute experiment. This might cause discharging of delayed ectopic impulses. However, this concept appears improbable when the long duration of this activity (two to five days) is considered. Adaptation to the conditions produced by the increased flow, and cessation of the discharge would be expected within a much shorter time. Excitation by products of necrosis appears to be the more probable late developing factor.

Summary

The anterior descending arteries of dogs were ligated aseptically and the resulting ectopic ventricular activity was studied almost continuously by electrocardiographic observations and frequent records.

By occluding the artery in two stages loss of animals by early ventricular fibrillation was prevented.

Following the final stage of occlusion there was a period of four and one-half to eight hours with little or no ectopic activity. After this latency, ectopic impulses developed rapidly, reaching the maximal frequency within ten to twenty-one hours. Typically, a high ectopic rate persisted through the first postoperative day and then subsided slowly, disappearing after two to four days.

The rectal temperature usually rose simultaneously with the rapid increase in ventricular

ectopic frequency, but consistent correlations between temperature and ectopic frequency are lacking.

Large gross infarcts resulted from the occlusions. In some hearts an external layer was spared. A very thin endocardial layer appears to be spared in all hearts. The earliest microscopic signs of necrosis have been found to become visible after a period similar in duration or only slightly longer than the latency for the rapid delayed rise of ectopic activity.

An attempt toward an analysis of the excitatory factors which probably produce ectopic impulses has been made. Cells within the boundary between the ischemic and non-ischemic tissues undoubtedly are rendered hyperexcitable by moderate ischemia, and this hyperexcitability probably is enhanced by catelectrotonus resulting from the injury potential.

Possible additional excitatory factors are sympatho-adrenal substances, histamine, and other substances formed or liberated during necrosis.

The delayed and rapid rise of frequency of ectopic beats which begins after four and one-half hours of occlusion or longer is evidence that new and intense excitatory influences are added after this long latency. This long delay together with the failure of added anesthesia to prevent the delayed rise is considered as evidence that the delayed excitatory factors are produced or released by processes of necrosis.

The possibility that a delayed increase in collateral circulation to the ischemic area may increase excitability and thereby contribute to the delayed ectopic activity is discussed. It is not believed to be an important factor.

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The Q-T Interval in Normal Infants and Children

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Because of renewed clinical interest in the Q-T interval and because of a need of normal values for an accompanying investigation in rheumatic fever, the Q-T was studied in 517 normal infants and children from birth to 13 years of age. A mean K of 0.404 for Bazett's formula and of 0.378 for Ashman and Hull's formula was obtained. With Bazett's curve approximating the data more closely, a Bazett's scattergram of the normal Q-T at varying heart rates was constructed. Although no difference in K value was noted between the sexes, significant differences were observed in certain age groups.

A SURVEY of the literature reveals that changes in the Q-T interval of the electrocardiogram have been mentioned in a variety of clinical conditions. Q-T prolongation has been observed in hypertension,[1] heart failure,[2] spasmophilia,[3] hypocalcemia,[4] hypopotassemia,[5] rheumatic carditis,[6] diphtheria,[7] quinidine intoxication,[8] nephritis,[9] and cretinism.[10] The Q-T has been used as an aid in differentiating pericardial effusion with heart failure from acute cardiac dilatation and failure, being prolonged in the latter condition.[11] It has also been found to be a good index of myocardial improvement during digitalis therapy,[12, 13] since the Q-T interval often regresses towards normal even before significant reduction in heart size occurs. This observation led to the concept that the Q-T reversal is evidence of the direct beneficial action of digitalis on the myocardium and not simply of diminution in heart size.[14] Similarly, others have felt that the Q-T interval is a more sensitive index of the state of the myocardium following exercise than is the heart rate.[15]

Abnormal shortening of the Q-T interval has received less study. It has been reported in hyperparathyroidism[16] and also as evidence of digitalis intoxication.[17]

Although several workers[18, 19] have not found the Q-T interval of much clinical value, it is evident that there is a renewed and increasing interest in its clinical applications. This has been particularly true, recently, in rheumatic carditis[20, 21] and in electrolyte disturbances.[22–24] Obviously, the accuracy of these observations depends upon the knowledge of the normal values of the Q-T interval not only at varying heart rates but also in relation to age and sex.

Several studies have been done on the electrocardiograms of normal infants and children, but only a few included the Q-T interval. Bazett,[25] in his original paper in 1920, reported only 5 cases in infancy. In 1937, Hafkesbring, Drawe, and Ashman[26] published their measurements in 100 normal children. Then, in a more extensive study in 1942, Ashman[27] included these same 100 and added 126 more, making a total of 226 children studied. However, he admitted that he did not have enough cases in infancy. Later reports by Savilhati[28] and Mannheimer[29] were based on 165 and 118 healthy children, respectively. Only a few infants were included in these two reports. The only extensive study of the subject in infancy is that of Nadrai,[30] who analyzed the electrocardiograms of 50 premature, 100 newborn, and 250 older infants. This study, however, fails to present the situation in the remaining years of childhood.

A more complete study, which would include both infancy and childhood and which would be done by the same observers, seemed especially warranted in view of the renewed interest in the clinical applications of the Q-T interval in pediatric practice; the present study was therefore undertaken. For an additional

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and more specific purpose, it was carried out to provide normal values for an accompanying investigation of the Q-T in rheumatic fever.[31]

Clinical Material and Method

This study is based on the electrocardiograms of 517 normal infants and children seen at the Boston Lying-In Hospital, the Department of Maternal and Child Health of the Harvard School of Public Health, and the Children's Hospital of Boston. The subjects ranged in age from birth to 13 years inclusive. There were 29 newborn infants, 78 older infants, and 410 children from the ages of 1 to 13 years.

In all instances these children were considered to have a normal cardiovascular system on the basis of negative findings in physical examination and history. Those at the Children's Hospital were seen for a variety of conditions totally unrelated to the heart.

The Q–T measurements were all made by one of us (M.M.A.), using a special reflectoscope to obtain more accurate measurements. By means of this device the electrocardiogram was projected on white paper and magnified at least ten times its actual size. In this way, the difficulty often met in the determination of the start of the Q wave as well as the end of the T wave was lessened appreciably. Measurements were thus obtained to the nearest 0.005 second. As a rule, no less than three cardiac cycles were analyzed and from these measurements the average Q–T and the average cycle length, R–R interval, were then derived. In instances showing significant sinus arrhythmia, these same measurements were done on more than three cardiac cycles, always including the shortest as well as the longest cycle lengths available. The measurements were done on Lead II unless there was a significant difference in the Q–T interval between this lead and either Lead I or Lead III due to an isoelectric Q wave in Lead II.

The electrocardiograms were taken with the infant or child lying supine in bed. They were recorded by means of the Sanborn electrocardiograph, generally the direct-writing Viso-Cardiette and in some in-

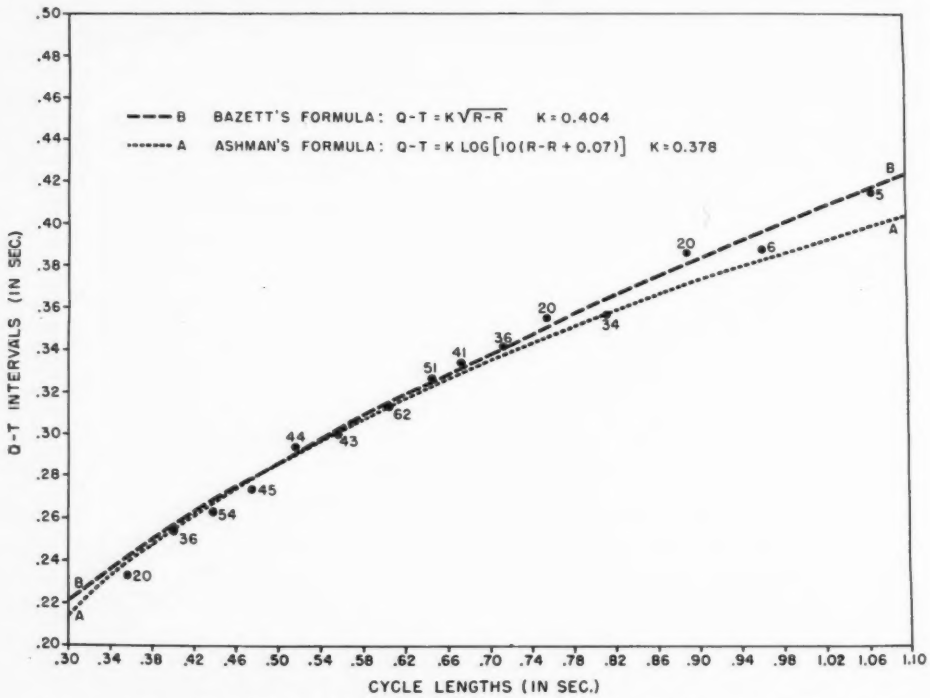

Fig. 1.—Q-T and R-R Relationship-Points of Entire Series at Varying Heart Rates. Each point represents the average Q-T plotted against the average R-R, at increments of 0.04 second in the R-R interval, except for R-R intervals above 0.82 second where the points are plotted at increments of 0.08 second in the R-R interval. Numbers indicate the number of cases included in each average. Curves are drawn on the basis of Bazett's and Ashman and Hull's formulas with the mean K values derived from the actual data.

stances the photographic Instomatic Cardiette. That both types of electrocardiographs give essentially identical records and can thus be jointly included in a common study has been recently demonstrated.[32]

Results

The 517 cases were divided into groups according to their cycle lengths, as measured by the R-R interval. Except for those with an R-R interval greater than 0.82 second, the subjects were grouped together within an increment of 0.04 second in the cycle length, starting from 0.30 second. The cases with slower heart rates were grouped at increments of 0.08 second in the cycle length because of the relatively fewer cases in this range. The average Q-T and R-R intervals for each group were determined. Then the average Q-T value was plotted against the average R-R value, as shown in figure 1. With each point in the graph is also indicated the number of cases from which the average Q-T and R-R figures were derived. It can be seen that except for the three slower rates there is a uniform and adequate distribution of the material throughout the graph.

An attempt was then made to find out whether there is any single formula or curve that can satisfactorily express the pattern of the Q-T and R-R relationship of our entire series. The two most widely accepted formulas, namely, Bazett's and Ashman and Hull's, were tested. The constant K was determined for each subject, both with Bazett's formula as well as with Ashman and Hull's. This was done by dividing the Q-T interval by $\sqrt{\text{R-R}}$ for Bazett's constant and by $\log[10(C + 0.07)]$ for Ashman and Hull's constant. The resultant mean K for Bazett's formula was 0.404 with a standard deviation of 0.026 and a coefficient of variation of 6.4 per cent. With Ashman and Hull's formula, the mean K value was found to

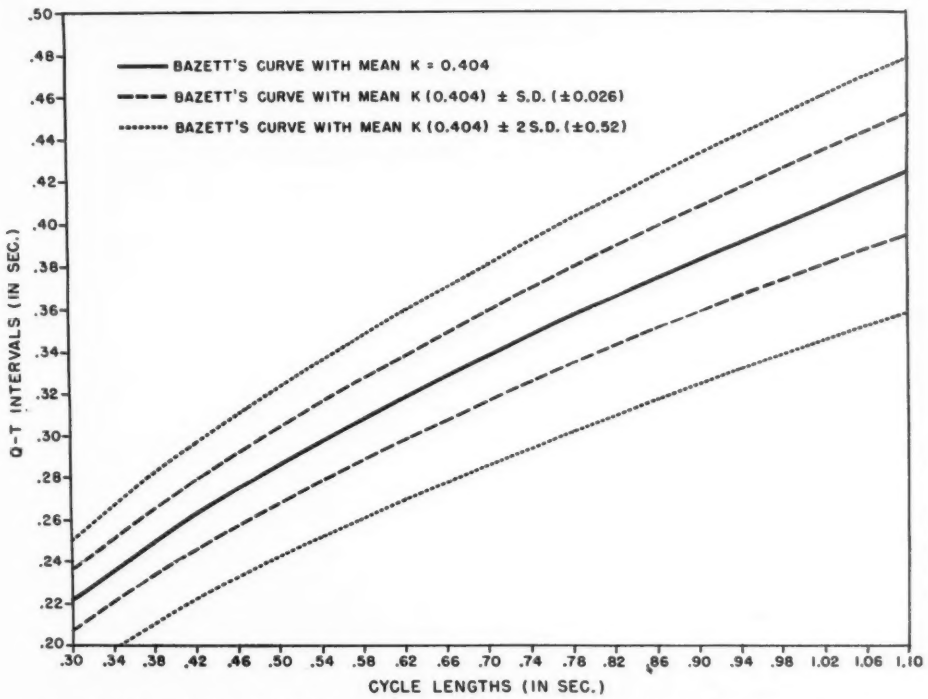

Fig. 2.—Normal Spread of Q-T and R-R Relationship. Using Bazett's formula and the mean K value derived from the data and its standard deviation, this diagram represents the normal spread of our cases. Middle curve is mean curve. Area between broken lines includes 73 per cent of the cases, and wider area between dotted lines includes 95.6 per cent of cases.

be 0.378 with a standard deviation of 0.025 and a coefficient of variation of 6.6 per cent. Curves were then constructed, using the mean K values for each formula. It is evident that both curves (fig. 1) approximated satisfactorily the average points, although Bazett's curve fitted them somewhat more closely than Ashman and Hull's curve.

With the values for Bazett's formula as derived from our data, the normal spread of the area of spread includes 95.6 per cent of all cases. Only 4.4 per cent of the entire series fell outside this area; that is, 11 cases above and 12 cases below.

As a corroborative analysis, the frequency distribution of the individual K values was also plotted (fig. 3). As already mentioned, the mean K for Bazett's formula was 0.404 while that of Ashman and Hull was 0.378. Although the general configuration of these two curves

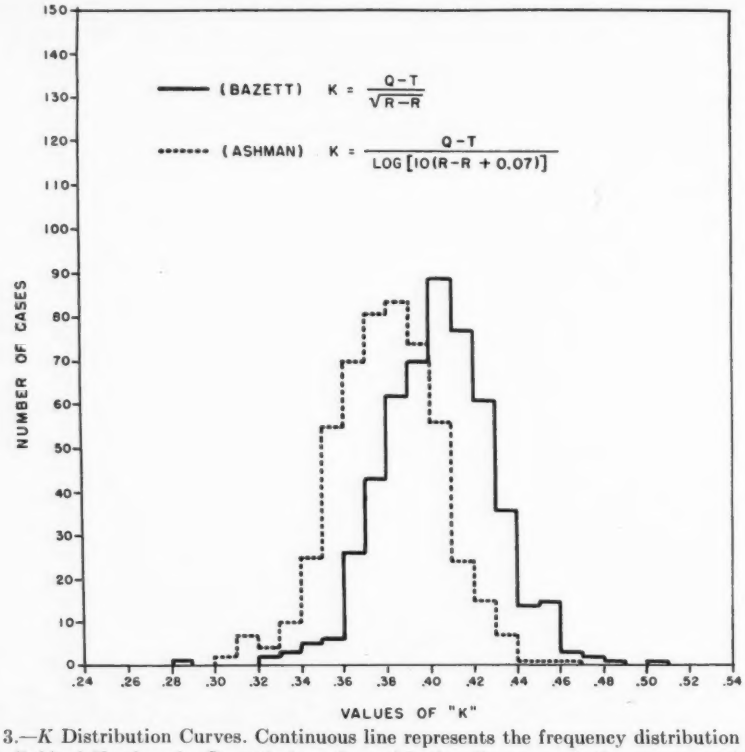

FIG. 3.—K Distribution Curves. Continuous line represents the frequency distribution polygon of the individual K values for Bazett's formula, and broken line presents the same material on the basis of Ashman and Hull's formula.

entire series was next studied. The result of this analysis is shown in figure 2. Curves above and below the average curve were constructed, using K values of once and twice the standard deviation over and below the mean K. The area covered by the curves close to the average curve includes 73 per cent of our cases, leaving 80 cases below the lower margin and 60 cases above the upper margin of this area. If twice the standard deviation is used, then the wider was very similar in both instances, Bazett's K distribution curve tends to include a greater number of cases close to or within its standard deviation—this in spite of the fact that the extremes on both sides of the graph belong to Bazett's K. In any event it is obvious that no single K value is applicable to both formulas.

The next point studied was the possibility of a further differentiation in this general pattern of the Q-T and R-R relationship and K values

through the various ages of infancy and childhood. By plotting the individual Q-T and R-R points along the mean curves according to both Bazett's and Ashman and Hull's formulas, it was found that a certain distribution pattern was consistently followed by individuals within a given age group, but that these age groups differed from each other: in some the Q-T and R-R relationship-points uniformly fell close to, in others below, and in still others above the mean curves. The individual K values were then compared to the mean K values in both formulas. Again, the same age group pattern was observed. Table 1 illustrates these results on the basis of the study of the individual K values as related to the mean K, following Bazett's formula. The other tables and figures showing this entire set of analyses are not included here in view of the identical results obtained. Except for the 1 to 4 month age group, the value for K is shorter in the younger ages and progressively longer in the older age groups. The differences in K values among these age groups are statistically significant as indicated by the coefficient of variation. This would suggest a certain pattern of the Q-T and R-R relationship, hence also of the K value, that is consistently followed and probably peculiar to specific age groups in infancy and childhood.

TABLE 1.—*Bazett's K in Different Age Groups*

Ages	Mean "K"	Standard Deviation	Coefficient of Variation
0–Below 1 month	0.386	0.019	4.9%
1–4 months	0.410	0.024	5.9%
5 months–1 year	0.391	0.022	5.6%
2–5 years	0.401	0.023	5.7%
6–13 years	0.416	0.025	6.0%
0–13 years	0.404	0.026	6.4%

Finally, table 2 shows that there is no significant difference in K values between the sexes. This situation is unlike that in adults where women have a higher K value than men, indicating that women tend to have a longer Q-T interval than men for the same heart rate. This lack of significant difference between the sexes in our series is evident not only from the overall figures but also from the mean figures for the various age groups. There is an almost equal distribution of cases between the sexes in our series in the total number as well as in the different age groups.

As far as individual cases are concerned, 8 had Q-T intervals longer than 0.40 second, 2 of which were 0.44 second. These cases were found in the older ages with longer cycle lengths. The slowest heart rate among these 8 subjects was that of a 12 year old child who had a cycle length of 1.18 second and a Q-T interval of 0.415 second. At the other extreme, 5 cases had Q-T intervals of 0.22 second or less. The shortest was 0.21 second and was found in a 4 month old infant with a cycle length of 0.39 second. This was not the fastest heart rate in the entire series, however, the shortest cycle length being 0.326 second in a 1 month old infant with a Q-T interval of 0.225 second.

TABLE 2.—*Bazett's K by Age Groups and Sexes*

Ages	Males		Females	
	No. of Cases	Mean "K"	No. of Cases	Mean "K"
0–Below 1 month	13	0.387	13	0.381
1–4 months	13	0.411	15	0.407
5 months–1 year	56	0.391	55	0.388
2–5 years	89	0.396	65	0.397
6–13 years	102	0.415	96	0.410
0–13 years	273	0.403	244	0.400

On the basis of Bazett's formula, the largest K value was that of 0.50 in a 9 year old child with a cycle length of 0.52 second and a Q-T interval of 0.36 second. The smallest K was 0.289 in a 6 month old infant with a cycle length of 0.465 second and a Q-T interval of 0.225 second.

DISCUSSION

The value of the measurement of the time duration of ventricular systole as a criterion of myocardial efficiency is agreed upon by physiologists.[25, 33] Garrod[34] was the first to point out the relationship between heart rate and the duration of ventricular systole. Although several other factors have since then been found to affect the duration of systole, all workers

agree that the cardiac cycle length is the most important one.[35] To express this relationship in terms of the Q-T and R-R intervals of the electrocardiogram, several empiric formulas have been proposed. The most widely used are those of Bazett and of Ashman and Hull. Bazett's formula, similar to many others, is a somewhat linear or curvilinear formula, while that of Ashman and Hull is the only logarithmic one. The latter workers feel that a logarithmic formula should be a better one because of the closer relationship between logarithmic formulas in general and many biologic processes.[26] On the other hand, if a linear or curvilinear formula can be just as satisfactory as a logarithmic one, the former is certainly a much simpler and more practical guide.

Among the various simple formulas, Bazett's is probably the simplest. Using the cube root rather than the square root of the cycle length, Fridericia[36] proposed an almost identical formula to that of Bazett: $Q\text{-}T = K\sqrt[3]{C}$. These two formulas have been found to be substantially correct by several other workers,[37–42] except for some changes in the absolute value for K to suit the actual data of individual series. However, a few observers have introduced completely different formulas. Adams,[43] for instance, proposed the formula, $Q\text{-}T = 0.1536\ R\text{-}R + 0.2462$, for men and $0.1259\ R.R + 0.2789$ for women. More recently, Schlamowitz[44] introduced the formula, $Q\text{-}T = 0.205\ C + 0.167$, while Lung[45] favors the formula, $Q\text{-}T = 0.2\ R\text{-}R + 0.12 \pm 0.04$.

In the present study, only Bazett's and Ashman and Hull's formulas were tested chiefly for two reasons: first, because they are the two most widely used, and second, because such an analysis would tell us whether a more complicated logarithmic formula is needed rather than a simpler linear or curvilinear one. From the results in figure 1 it is evident that there is no real need for a logarithmic formula and that Bazett's simple formula actually gives a slightly more satisfactory approximation of our actual measurements. The validity of this analysis is confirmed by the fact that the mean value of 0.378 for Ashman and Hull's K, as derived from our data, fits exactly Ashman's more recent observation[46]; namely, that the mean K value for children is closer to 0.38 than to the original Ashman and Hull's figure of 0.375 for both men and children. With Bazett's formula giving a closer approximation, it becomes imperative to know the true value for Bazett's constant in these younger ages. We believe that the present study, derived from a series that is large and evenly distributed throughout the entire span of infancy and childhood, furnishes this data for the first time. Our figure is significantly different from those that Bazett found in adults (men, 0.37; women, 0.40).

It is equally important to know the normal spread of individual cases around this normal mean value or curve. Ashman and Hull furnished figures for their upper limits of normal, using their formula and considering identical K values for men and children. Bazett, on the other hand, did not furnish similar figures for adults, nor could he do so for children because of an insufficient number of cases. Our figure for Bazett's mean K differs significantly from various figures in the literature that have been employed for the upper limits of normal in evaluating individual cases on the basis of Bazett's formula. Our results also demonstrate that the K values in the younger ages differ from those generally accepted for adult men.

Other investigators[3, 18, 47] have preferred to approximate the normal spread from scattergrams of their normal figures, the mean curve being constructed by simple inspection of these figures. This is probably an easier procedure but is less accurate than one in which curves are derived through a mathematical appraisal of the actual measurements. In any event such a graph for the normal spread is obviously a more practical guide for the evaluation of individual Q-T intervals than tabulated figures and prediction tables which may set too rigid criteria for individual cases. For this reason figure 2 was constructed. Such a diagram not only relates an individual case, indicated by its Q-T and R-R relationship-point, to the mean normal curve but also to the areas of normal spread. The fact that such areas are wide in young children is an important point to be considered. In fact, even with the wider area of spread, 4.4 per cent of our cases still fell beyond it. These findings emphasize the need for a less rigid

attitude in evaluating the Q-T interval in infancy and childhood as perhaps in contrast to adults. This is even more important when the Q-T interval may be the only apparent abnormality in an individual case.

Finally, the differences in K values observed for the arbitrary age groupings in table 1 are of special interest. While statistically significant, they may not be exclusively due to a peculiar and specific pattern for certain ages of infancy and childhood. These age groupings were arrived at on the basis of the relationship of the Q-T and R-R points as well as the individual K values to the mean curves and mean K values, respectively, of Bazett and of Ashman and Hull. Evidently, while both curves are satisfactory approximations of our actual figures, neither of them is identical with our data. This technical factor may partly explain the resulting age group deviations. How much deviations are due to real age peculiarities and how much to incidental apparent differences as a result of the method herein followed can be ascertained only by constructing a new formula derived from our figures.

Obviously, a new formula for this purpose alone is not indicated, especially when the two formulas tested proved to be satisfactory. Furthermore, another formula added to the many already found in the literature cannot possibly clarify, much less simplify, the Q-T problem. From our observations, therefore, we may suggest that evaluation of individual Q-T intervals in infancy and childhood can be satisfactorily done on the basis of the over-all figures for Bazett's K and the diagram for the normal spread in figure 2. Only in instances where greater accuracy is needed and in studies involving certain age groups of infants or children may the age group figures in table 1 have to be followed.

Summary and Conclusions

The Q-T interval was measured in 517 normal infants and children from birth to 13 years of age inclusive. Its relationship to the cardiac cycle length was studied on the basis of both Bazett's and Ashman and Hull's formulas. Although curves from both of these two formulas approximated the data well, Bazett's curve fitted them somewhat more closely. The values for the mean K in these two curves were 0.404 with a standard deviation of 0.026 for Bazett's formula and 0.378 with a standard deviation of 0.025 for Ashman and Hull's formula.

The spread of the normal Q-T, as related to the heart rate, can be expressed by the diagram with areas bounded by curves constructed with K values of the mean K plus and minus once and twice the standard deviation. In such a diagram, 73 per cent of all cases fell within the narrower area of spread and 95.6 per cent within the wider area.

Differences in the K values were noted in certain age groups, suggesting the possibility of some age peculiarities of the Q-T and R-R relationship. These variations may have to be considered for purposes of greater accuracy as well as for studies involving specific age groups in infancy and childhood.

There was no significant difference in K values between the sexes.

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The Q-T Interval in Rheumatic Fever

By Ernest Craige, M.D., Mariano M. Alimurung, M.D., Edward F. Bland, M.D., and Benedict F. Massell, M.D.

In 143 rheumatic children the Q-T interval was found to be normal in those with quiescent rheumatic heart disease. In 29 with fatal pancarditis the average Q-T was above the average normal, though not beyond the upper limit of normal. Although parallel changes in the Q-T interval and the clinical manifestations of rheumatic fever occurred in about 66 to 75 per cent of cases, there were significant number of instances where changes in the Q-T and in the clinical course of the disease were in opposite directions.

THE DIFFICULTIES encountered in the diagnosis of rheumatic fever are well known. Frequently the history offers only questionable evidence of arthritis, chorea, or cardiac involvement, and physical examination may fail to demonstrate signs of active rheumatic fever. If the presence of carditis can be established, the diagnosis is immediately placed on a more certain foundation, and, at the same time, one is provided with information of some prognostic value.[1] In recent years, therefore, almost every feature of the electrocardiogram has been explored for evidence of cardiac involvement in rheumatic fever.[2–4] The demonstration of delayed A-V conduction, S-T and T-wave changes or arrhythmia has often been of value in this connection.[5] More recently, attention has been directed toward the Q-T interval in rheumatic fever.

The duration of electrical systole as measured by the Q-T interval is known to be prolonged in a variety of pathologic states.[6] In certain instances a definite lengthening of the Q-T interval has been seen in rheumatic carditis.[7, 8] In an analysis by Drawe and associates[7] of the electrocardiograms of 100 children with rheumatic heart disease, of whom 25 had acute rheumatic carditis, prolongation of the Q-T interval was demonstrated in 25. No statement was made as to whether the patients with prolongation of the Q-T interval were the same as those with evidence of carditis. In a control group of 100 children, only 4 exceeded the upper limit of normal as defined by Ashman and Hull.[9]

Recently, further claims for the usefulness of the Q-T interval in separating quiescent rheumatic patients from those with carditis have been made by Taran.[10, 11] He has studied a group of 100 rheumatic children, in half of whom the disease was inactive. The remaining patients presented evidence of active rheumatic fever and carditis. The duration of the Q-T interval normally is dependent upon the heart rate. Hence, Taran made use of Bazett's observation[12] that the relation of the Q-T to the R-R interval can be expressed by the formula, $\frac{Q\text{-}T}{\sqrt{R\text{-}R}} = K$. For purposes of comparing the Q-T intervals of various individuals, normal and abnormal, at different heart rates, Taran has redefined the ratio of Q-T:R-R as the corrected Q-T interval, namely, $Q\text{-}T_c$. Thus, $Q\text{-}T_c = \frac{Q\text{-}T}{\sqrt{R\text{-}R}}$.

There was a distinct separation in Taran's cases of the inactive from the active group. When the $Q\text{-}T_c$ of each patient was recorded as a point on a graph in which the upper limit of normal for $Q\text{-}T_c$ was indicated by a horizontal line, all of the points for the patients in the active group fell above this line, whereas all except one of the points for the inactive group fell below the line. Taran has chosen the figure 0.405 as the upper limit of normal for Q-T$_c$. For the source of this figure, he cites Ashman and Hull.[9] The latter authors, however, have used this figure not in the Bazett formula but in Ashman's formula,[9] $Q\text{-}T = K \log[10(R\text{-}R$ –

From the House of the Good Samaritan, Children's Medical Center, Boston, Mass.

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0.07)]. That the value of K or Q-T_c is not interchangeable in the two formulas has been previously demonstrated.[13]

Furthermore, Taran points out that the average duration of Q-T for his quiescent cases is very close to the average Q-T of 0.325 second found by Hafkesbring and associates[14] in normal children. The latter authors also found the average corresponding heart rate for their normal children to be 92.7, a figure equivalent to an R-R interval of 0.647 second. If one applies the average Q-T of 0.325 and the average R-R of 0.647 to Taran's formula, the average Q-T_c is found to be 0.404. Hence, it seems improbable that the upper limit of normal for Q-T_c would be only 0.405.

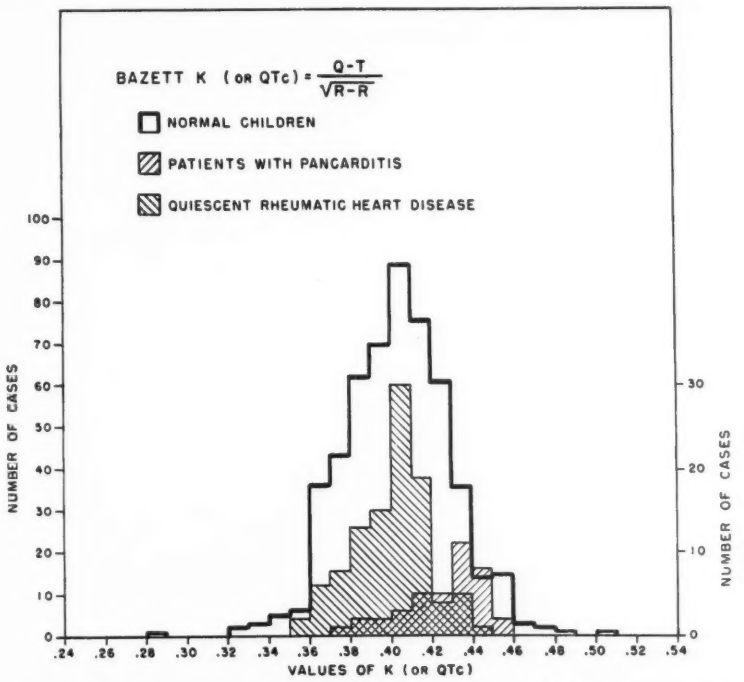

FIG. 1.—Q-T_c distribution curves of fatal and quiescent rheumatic patients compared with the K distribution curve for normal children.

CLINICAL MATERIAL AND METHOD

The present study was undertaken in order to determine the usefulness of the measurement of the Q–T interval in rheumatic fever. It has been recommended by Ashman[15] that along with any observation of the Q–T in rheumatic children a comparable group of normals be studied. The normals should afford controls of suitable age and environment. Our normal group has been previously reported.[13]

The rheumatic fever subjects of this study were ward patients at the House of the Good Samaritan. They include 63 boys and 80 girls in the age group of 7 to 14 years. The patients fell into two main groups:

(A) Patients with quiescent rheumatic heart disease. This group is composed of 102 patients who at the time of discharge from the hospital showed definite evidence of rheumatic heart disease with or without appreciable cardiac enlargement but with no clinical or laboratory evidence of rheumatic activity.

(B) Patients with active rheumatic fever. This group includes 29 patients with fulminating pancarditis resulting in death and 29 others with varying lesser degrees of active rheumatic disease. Among the latter were 17 patients also studied during a quiescent stage of their illness, and who, therefore, were also included in Group A above.

Only those electrocardiograms which showed sharply defined T waves were used. Usually measurements were made on standard Lead II, using average figures for Q–T and R–R intervals from a sequence of 8 to 12 cardiac cycles to minimize the

effects of sinus arrhythmia. A special reflectoscope[13] was used to magnify the tracings and facilitate accurate measurement.

Results

A. Patients with Quiescent Rheumatic Heart Disease

This group is composed of 102 children who at the time of their discharge from the hospital presented no clinical or laboratory evidence of rheumatic activity, but all of whom, on physical examination, showed definite signs of rheumatic heart disease. Repeated electrocardiograms were taken during their hospitalization, which varied from one to fourteen months, and the final tracing, taken just prior to their discharge, was used in this study. The Q-T_c for this group varied from 0.353 to 0.442 and averaged 0.395. The latter is slightly below the figure 0.404, the average value for our control group.[13] Figure 1 shows the distribution of the values for Q-T_c of these quiescent rheumatic individuals superimposed on the curve of normal children of all ages. The shape of the curves is similar. The actual values for Q-T as measured—not corrected by any formula—are shown by the solid dots in figure 2. The individual measurements fall well within normal limits.[13]

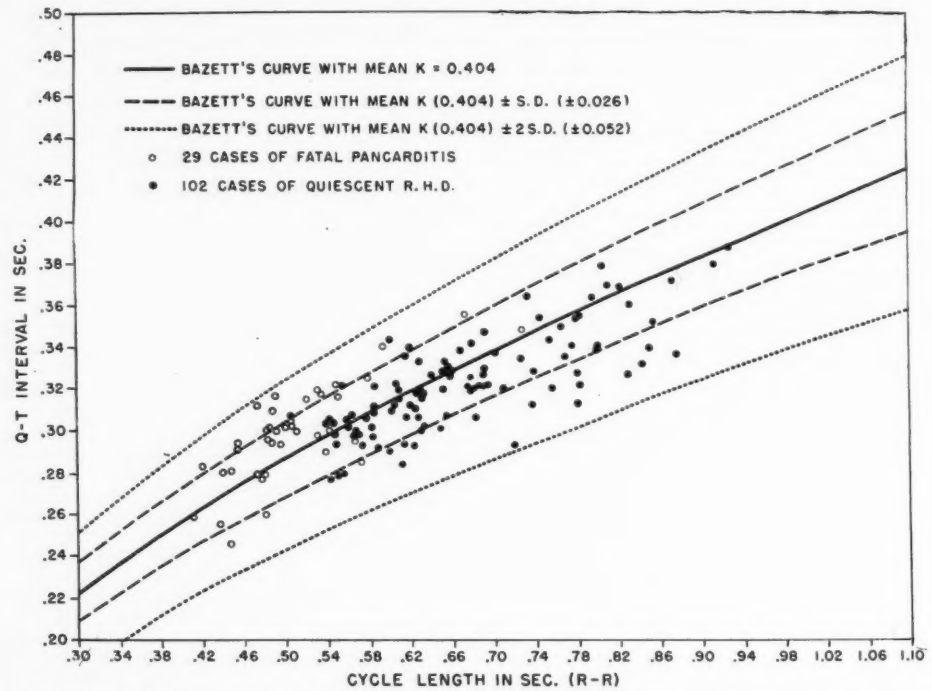

Fig. 2.—Q-T intervals of 39 electrocardiograms of 29 fatal cases of rheumatic pancarditis (open circles) and of 102 patients with quiescent rheumatic heart disease (dots) plotted over normal curves with mean K of 0.404 as determined by Alimurung and co-workers[13] and standard deviations from the mean, indicating the upper and lower limits of normal.

B. Patients with Active Rheumatic Fever

For the purposes of analysis the patients composing this group have been divided into three subgroups; namely, a fatal group, a group that was observed during the subsidence of rheumatic activity, and a group that was studied during rheumatic recurrence. There is, however, some overlapping between the fatal and recurrent subgroups in that some of the patients who developed fatal recurrence have been included in both subgroups.

1. *Patients with Fatal Rheumatic Heart Dis-*

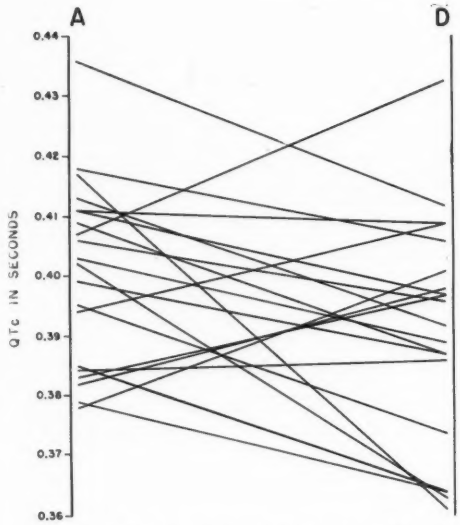

FIG. 3.—Q-T_c of 20 patients at the time of hospital admission (*A*) and at discharge from the hospital (*D*), after complete disappearance of rheumatic activity.

ease. A group of 29 fatal cases of rheumatic fever was reviewed. In 21 of these the presence of acute pancarditis was demonstrated at autopsy. In the other 8 the fulminating clinical course and physical findings gave evidence of a similar process. Patients receiving digitalis at the time of the electrocardiographic study or during the previous three weeks were eliminated owing to the shortening effect of this drug on the Q-T interval.[16] Five patients receiving small doses of xanthines or salicylates were not excluded. The tracings used in this analysis were taken during the final overwhelming phase of rheumatic infection. The individual Q-T measurements are shown by the open circles in figure 2. It is evident that the patients with pancarditis in general had faster heart rates than those who were quiescent. The Q-T intervals of the patients with pancarditis, although somewhat longer on the average than those of the quiescent group, fell nevertheless

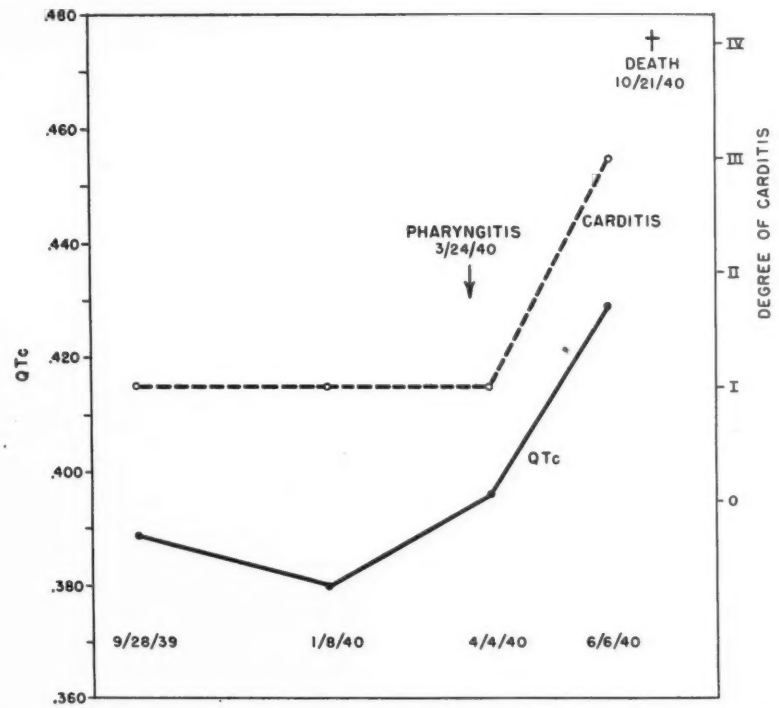

FIG. 4, *A*.—Relation of changes in corrected Q-T interval (Q-T_c) to the clinical course of two patients who developed fatal recurrence of rheumatic fever following streptococcal pharyngitis (See fig. 4, *B*)

within normal limits. An analysis of the same data in terms of Q-T_c is shown in figure 1. Here the distribution of the Q-T_c of the pancarditis group is superimposed on the distribution curve of normal children of all ages. There is considerable overlapping of the two curves, but it is apparent that the fatal cases tend to have a somewhat greater Q-T_c than the normals. The average Q-T_c of 39 electrocardiograms of this fatal group is 0.419, which is statistically different from our average normal of 0.404.[13]

2. *Patients with Subsiding Rheumatic Fever.* The patients with active rheumatic fever included a group of 20 individuals who improved appreciably while under observation. These patients presented definite evidence of active rheumatic fever[1] on admission to the hospital, but on discharge, after an average of six months of hospitalization, they showed no clinical signs of rheumatic activity, and their sedimentation rate, hematocrit, and P-R interval were well within normal limits. At the time of discharge from the hospital, 10 of these patients still showed signs of rheumatic heart disease, and 10 did not.

The Q-T_c of the electrocardiograms taken at the time of admission, when there was unequivocal evidence of active rheumatic fever, were compared with those of the tracings taken just prior to discharge when all clinical and laboratory evidence of rheumatic activity had disappeared. As shown in figure 3, the Q-T_c fell during the period of subsiding rheumatic activity in 14 of 20 cases, but in 6 of them the Q-T_c became longer. The cases showing a rising Q-T_c included 3 with rheumatic heart disease and 3 with no evidence of heart disease at the time of discharge. It is of interest that at no time did any of the patients have Q-T_c measurements beyond the upper limit of normal.[13]

3. *Patients with Recurrent Rheumatic Fever.*

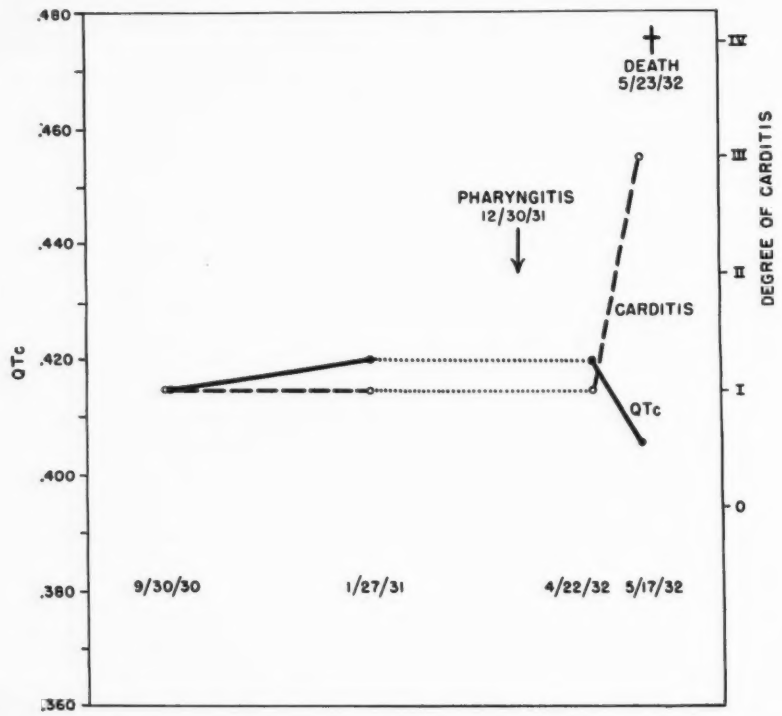

FIG. 4, *B*.—The dotted area represents the time when patient was symptom-free and outside the hospital, and no electrocardiographic data available then.

A group of 15 patients who suffered an exacerbation of rheumatic fever while under observation was also studied. In 6 of these patients, recurrent rheumatic fever resulted in death and they were therefore also included in the study of the fatal group. In the remaining 9, clinical evidence of moderately severe rheumatic activity appeared. Most of these patients were convalescent on the hospital wards during a streptococcal epidemic in 1939. In them it was possible to observe a recrudescence of rheumatic fever two or three weeks following streptococcal pharyngitis or tonsillitis. The Q-T interval was measured prior to the streptococcal infection, during it, and, two or three weeks later, at the height of the rheumatic process. An attempt was made to grade the activity of rheumatic fever in these cases in order to determine whether there was any correlation between it and the duration of the Q-T interval. Activity was graded from I to IV as follows: (I) mild (fever, arthritis, chorea, nosebleeds, rashes, nodules, elevated sedimentation rate); (II) moderately severe (changing murmurs, prolonged P-R interval, enlarging heart); (III) severe (congestive failure, evidence of pancarditis); (IV) fatal.

The clinical course of every patient was plotted according to the above criteria, indicating, roughly, his condition at the time of the electrocardiographic measurements, which were also plotted. In 3 cases out of the 15, a fairly accurate correlation could be observed between the patient's course and the fluctuations in his Q-T_c. An example of this type is shown in figure 4,*A*. Here, despite the fact that the patient was already suffering from the severe recurrence which led to his death, the Q-T_c did not reach an abnormal level at any time. In 8 other cases the correlation between the Q-T_c and the patient's clinical condition was not so close, but there was a tendency for the two to move in the same direction. As the patient's condition deteriorated, a slight lengthening of the Q-T_c occurred, and vice versa.

In 4 of the cases of recurrent rheumatic fever, on the other hand, the duration of the Q-T_c moved in a direction opposite to the patient's clinical course. An example of this type is seen in figure 4,*B*, where a fulminating carditis was accompanied by a shortening of the Q-T_c.

Discussion

Our results indicate that the Q-T interval in individuals with quiescent rheumatic heart disease is similar to that of normal individuals. In this respect, our findings agree with those of Taran[11] and Pokress and Goldberger.[17]

An analysis of the Q-T interval in rheumatic fever by the latter authors has been reported since our own studies were completed. Their results indicate that prolongation of the Q-T interval may occur in active rheumatic fever but does not invariably do so. They did not observe the very close relationship between the length of the Q-T interval and the presence of rheumatic activity that had been previously found by Taran.[11] From the data of Pokress and Goldberger, the Q-T_c of 50 active rheumatic patients can be determined. The average Q-T_c for this group is 0.409, a figure which is similar to our own average of 0.412.

Pokress and Goldberger found only 14 out of 50 patients with active rheumatic fever to have Q-T intervals which exceeded the normal upper limit accepted by these authors. If our criteria for normal subjects[13] are used, the number of their active rheumatic patients with prolongation of the Q-T interval is reduced to 10, since the upper limit for our normal controls is slightly higher than for theirs.

Our observations show a tendency for active cases to have a longer Q-T interval, on the whole, than normal subjects and quiescent cases. Fluctuations in the clinical conditions of the patient were often associated with alterations in the Q-T interval. Even in severe carditis, however, the Q-T interval did not exceed the upper limit of normal in a single case. Our studies, therefore, do not support the claims of Taran and Szilagyi[11] for the value of the Q-T interval as an accurate index of rheumatic carditis.

Summary and Conclusions

The Q-T interval of 143 rheumatic children between the ages 7 and 14 years was measured.

One hundred and two patients with quiescent rheumatic heart disease had Q-T intervals similar to those of normal children.

Twenty-nine patients with fatal pancarditis had Q-T intervals within the normal range,

but their average Q-T interval was slightly longer than that of normal control subjects.

In a group of patients with active rheumatic fever, changes in the Q-T interval occurred parallel with changes in the clinical condition in about two-thirds to three-fourths of the cases, but the opposite was also noted in a significant proportion.

Duration of the Q-T interval may be determined in the study of rheumatic patients as a part of an over-all estimate of activity of the disease. Its usefulness is minimized by technical difficulties in measurement and by the infrequency with which it is abnormal.

ACKNOWLEDGEMENT

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Relationship of Various Factors to the Degree of Coronary Atherosclerosis in Women

By ROBERT F. ACKERMAN, M.D., THOMAS J. DRY, M.B., AND JESSE E. EDWARDS, M.D.

The degree of coronary artery atherosclerosis present in 600 hearts obtained from women, 100 in each of the decades from 30 through 89 years, was determined by one observer. Coronary atherosclerosis increased with age until the eighth decade when the atherosclerosis tended to level off. Cardiac hypertrophy and diabetes were associated with increased degrees of atherosclerosis. Hearts from the undernourished exhibited less atherosclerosis than did hearts from average weight or overweight individuals. A comparison with data compiled on 600 hearts from men by White and associates has been included.

MOST of the reported pathologic data on the relation of degree of atherosclerosis to various factors have been derived exclusively from necropsy protocols.[1–3] Information available from such study indicates that the degree of coronary atherosclerosis progresses steadily with age; that men suffering from disease of the coronary arteries far outnumber women; and that among other factors hypertension, diabetes and the state of nutrition influence the formation of atheromatous lesions. There has been a tendency to emphasize the part played by age to the exclusion of other factors. Any one report on the relationship of age to the degree of coronary atherosclerosis often includes the observations of many individuals who wrote the protocols used in the particular analysis. A more reliable analysis would obviously be one in which the same observer studied all of the hearts reported on. This would yield a more standard evaluation of the degree of disease.

White personally examined the entire coronary tree in each of 600 consecutive hearts.[4] He found that the degree of coronary atherosclerosis reached a peak in the sixth decade of life. In later decades there was less severe atherosclerosis. His study was confined to male subjects and was reported by White, Edwards and Dry.[5] The present report deals with female subjects.

Abridgment of thesis submitted by Dr. Ackerman to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Medicine.

METHODS AND MATERIALS

Hearts from women in the age group 30 through 89 years were chosen for this study. One hundred consecutive hearts in each of the six decades were examined. The material parallels the study of White and associates[5] from the Mayo Clinic on hearts of men. The specimens used in the current study had been saved at the time of necropsy as a routine procedure. Hearts from patients dying from disease of the coronary arteries or from any other disease were not excluded.

Both left and right coronary arteries were studied in each heart by one of us (Ackerman). The left coronary artery consists of its main trunk and its anterior descending and circumflex branches. The right coronary artery consists of its main trunk and its marginal and posterior descending branches. Each of these six divisions was arbitrarily subdivided into proximal, middle and distal portions, except for the main left coronary artery which is usually less than 2.5 cm. in length and was considered too short for subdivision (fig. 1). The sixteen subdivisions of the coronary arteries so obtained were evaluated individually for the maximal degree of atherosclerosis present.

To establish the degree of atherosclerosis, cross sections of the arteries were made with a sharp knife at 3 mm. intervals. Actual grading was on a basis of 1 to 4, with 1 representing minimal sclerosis and 4 complete atherosclerotic closure of the lumen. The photomicrographs presented (fig. 2) are representative of the various grades of sclerosis and are reproduced through the courtesy of White and associates. It is important to stress that the maximal rather than the average degree of atherosclerosis was recorded for each of the sixteen subdivisions. This is defined as the *grade of sclerosis*. Grading was simplified by using in-between points such as 2.5 when the degree of sclerosis fell midway between 2 and 3. The grading is identical with that used in the study by White and associates. Grade 1 is used

to designate less than 25 per cent reduction in the diameter of the lumen, grade 2 represents 25 per cent closure of the luminal diameter, grade 3 represents 50 per cent closure and grade 4 represents 100 per cent closure of the lumen. When the vessel was occluded by a clot, only the underlying sclerosis was used as the basis for grading; the clot was not considered.

The cardiac weight, the principal and contributing causes of death and any sign or symptom leading to a clinical suspicion of coronary disease were recorded from data in necropsy protocols and abstracts of the clinical records. To determine the effect of emaciation and obesity on atheromatous deposits the state of nutrition as noted in each necropsy protocol was recorded. The presence of diabetes was also noted.

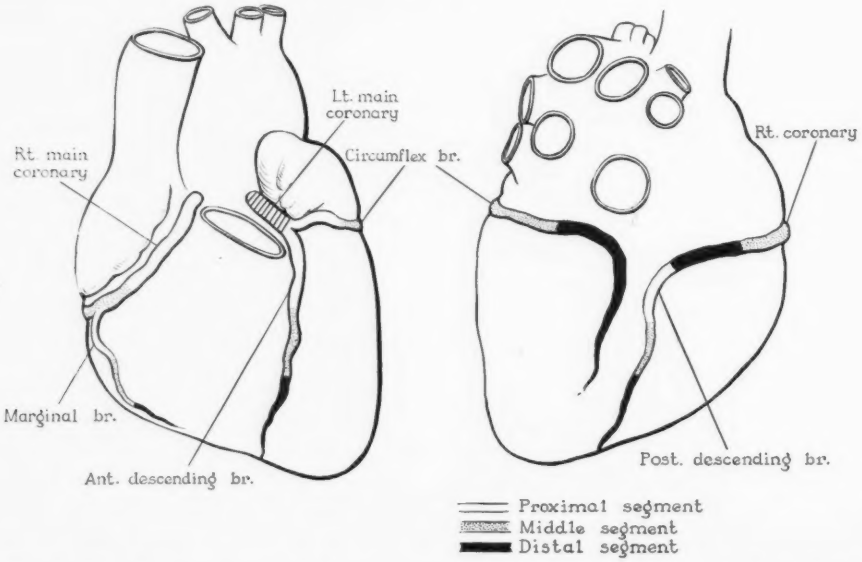

FIG. 1.—The sixteen segments of the coronary arteries in which the degree of atherosclerosis was determined.

RESULTS

Correlation of the Degree of Coronary Atherosclerosis With Age

In the study made by White, Edwards and Dry[5] an analysis was made to determine the degree of atherosclerosis in each of the sixteen portions of the coronary arterial tree. With one exception these authors found a higher grade of sclerosis in the proximal part in five of the six major divisions (anterior descending, left circumflex, right main, right marginal and posterior descending) in every decade. The one exception was a higher grade of sclerosis in the middle part of the main right coronary artery than was present in the proximal part in the seventh decade. The grade of sclerosis was least in the distal part of all five divisions in every decade. Since the trunk of the left coronary is less than 2.5 cm. in length, it was not divided into parts as were the other five divisions.

In this study a similar analysis was made. With but two exceptions the proximal part in five of the six major divisions had a higher grade of sclerosis than did the middle or distal parts in each decade. One exception occurred in the left circumflex artery where the grade of sclerosis in the middle part was greater than that in the proximal part in the eighth and ninth decades. The other exception occurred in the main right coronary artery; a higher grade of sclerosis was present in the middle part than was present in the proximal part in the eighth decade. The grade of sclerosis was least in the distal part of all five divisions in every decade.

Average Grade of Sclerosis in the Six Main

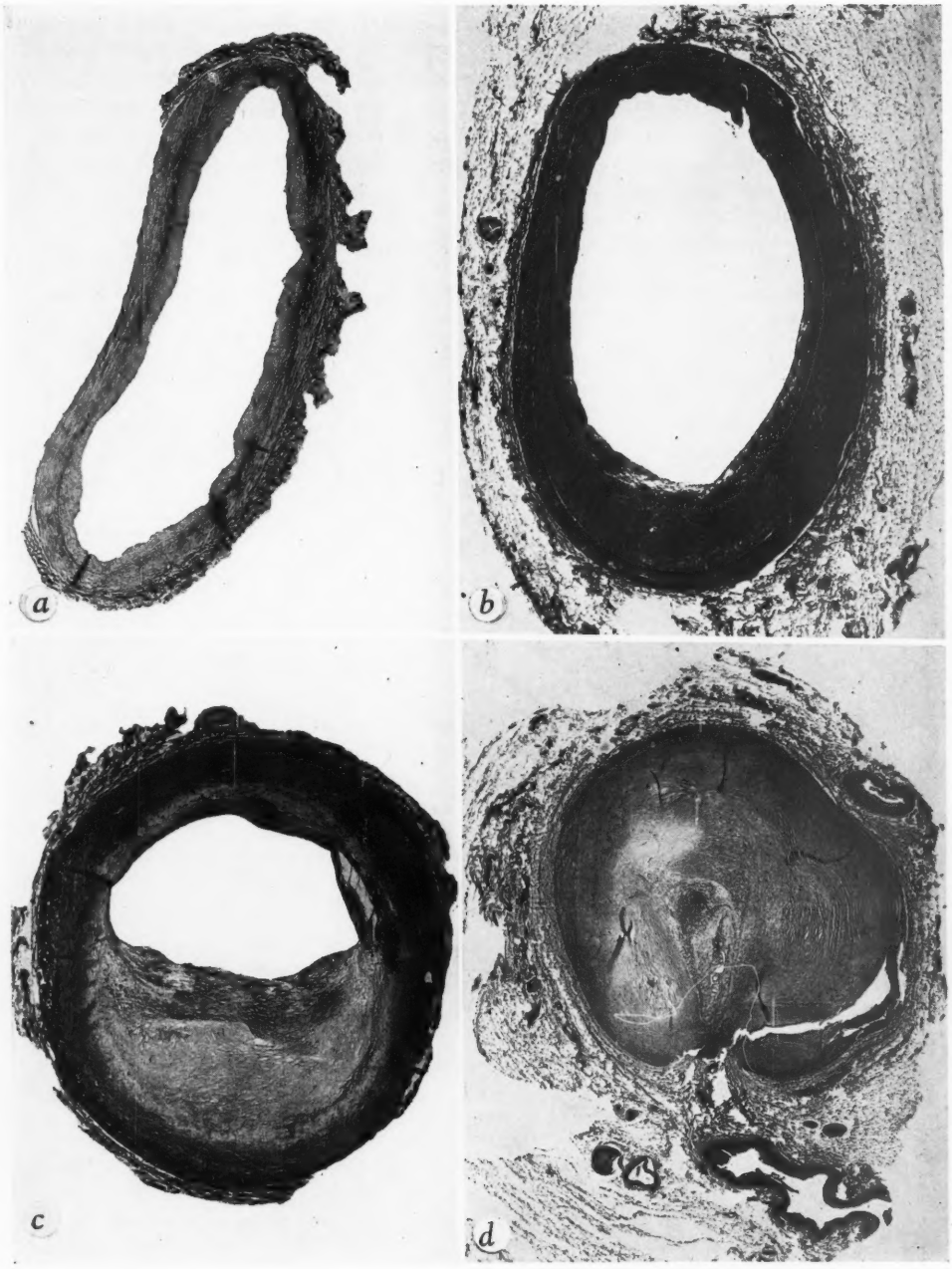

FIG. 2.—Examples of the four grades of sclerosis in coronary arteries. Sections stained with hematoxylin and eosin. *a*, grade 1(× 30); *b*, grade 2(× 22); *c*, grade 3(× 15); and *d*, grade 4(× 15).

Divisions. The highest grade of sclerosis was determined in each of the sixteen parts of the coronary arterial tree as described in a previous paragraph. To determine the highest grade of

sclerosis in each of the six main divisions (left main, anterior descending, left circumflex, right main, right marginal and posterior descending), one value, the highest grade of sclerosis occurring in the proximal, middle or distal part of that vessel, was used.

Atheromatous deposits involved the six main divisions in the following descending order of severity: anterior descending, right main, left circumflex, left main, posterior descending and marginal (fig. 3). In the anterior descending branch the grade of sclerosis increased from 1.28 in the fourth decade to 2.75 in the ninth decade. The grade of sclerosis in the main right coronary artery increased from 1.19 in the fourth decade to 2.48 in the eighth decade; it was 2.46 in the ninth decade. The general trend was a steady consistent rise from the fourth decade through the eighth decade in all divisions of the coronary arterial tree. In the ninth decade there was a tendency to level off. In three divisions in the ninth decade the grade of sclerosis was equal to or less than that in the eighth decade. In three other divisions there was a rise from the eighth to the ninth decade which, however, was less marked than between earlier decades.

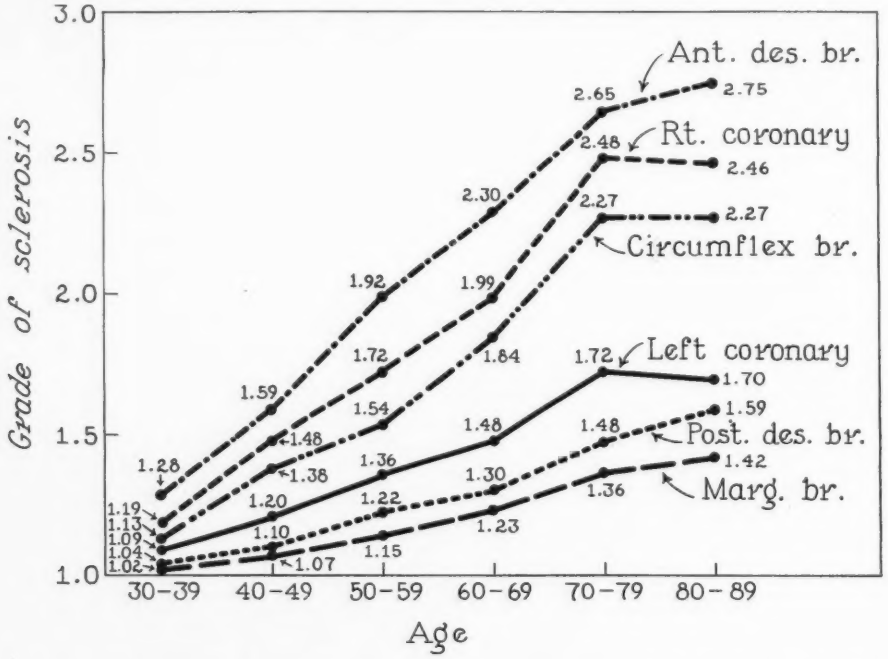

FIG. 3.—The average of the maximal degrees of atherosclerosis for each of the six major divisions of the coronary arteries by decades. The value for the greatest degree of coronary sclerosis present in either the proximal, middle, or distal part of a major division was taken as the grade of sclerosis for that division. The one hundred values thus obtained in each decade were then added and the sum divided by 100 (the number of hearts in each decade) to obtain the average grade of sclerosis for a major division.

Percentage of Hearts With Severe Sclerosis. Five per cent of hearts in the fourth decade had a severe degree of atherosclerosis (grade 3 or higher) at some point in the coronary arterial system (fig. 4). After the fourth decade the rise in the curve is accentuated with the passing of each ten-year period up to the eighth decade. By the eighth decade 60 per cent of the hearts showed a severe degree of involvement. Like-

wise, 60 per cent of hearts were so involved in the ninth decade, suggesting a leveling off after the eighth decade.

Comparison of Right and Left Coronary Arteries. A greater number of hearts had severe sclerosis in the left coronary artery than in the right (fig. 4). This discrepancy was most marked in later decades. In the eighth decade 52 per cent of the left coronary arteries and only 36 per cent of the right coronary arteries were involved by a severe degree of atherosclerosis (grade 3 or greater).

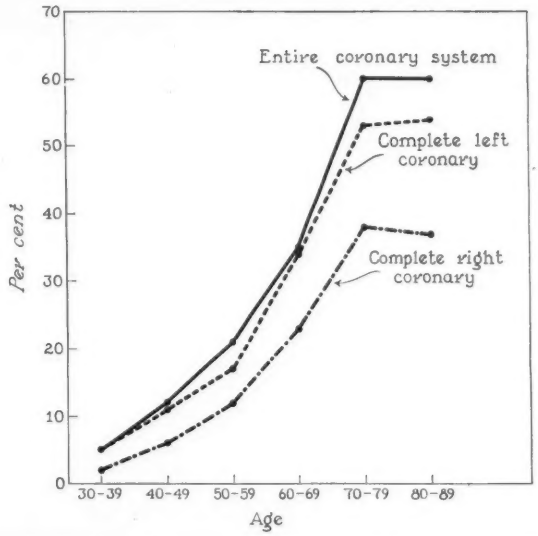

FIG. 4.—The percentage of hearts showing at some point in the coronary arterial system a degree of sclerosis of grade 3.0 or greater. Comparison is made between the complete left coronary, the complete right coronary, and the entire coronary artery system, the last-mentioned representing all hearts with grade 3 or greater sclerosis in the complete left coronary plus those hearts with less than grade 3 in the complete left coronary but with grade 3 or more somewhere in the complete right coronary artery.

The "Average" Grade of Coronary Atherosclerosis. The average grade of sclerosis for *each heart* was determined by adding the values for grade of sclerosis in each of the six main divisions of the coronary arterial tree and dividing by six. The figures thus obtained for all the hearts in a given decade were added together and divided by 100 (the number of hearts in each decade). The result was an "average" of the grade of sclerosis for the hearts in that decade (fig. 5). In essence the values obtained represent a composite of those of figure 3. The data are presented in this fashion because in all subsequent calculations which have been made to evaluate the influence of factors other than age on coronary atherosclerosis, the average grade of sclerosis has been used for comparison. Hereinafter the term "average grade of sclerosis" will refer to figures obtained in the manner used to construct figure 5.

Relation of Cardiac Weight to Coronary Atherosclerosis

The data were analyzed to determine if cardiac weight had any relation to the grade of sclerosis. According to Smith,[6] more than 75 per cent of the hearts from women with hypertension weigh more than 350 Gm; in the female sex nearly all normal hearts weigh less than 350 Gm.[7]

The data were studied to see whether there was any correlation between cardiac weight and the average grade of coronary artherosclerosis (tables 1 and 2). Inspection of these tables

leaves little doubt that the heavier hearts had a greater degree of atherosclerosis than did lighter ones. As shown in table 1 the heavier hearts had a 15 to 43 per cent higher average grade of sclerosis than did the lighter ones. In table 2 it is shown that the heavier hearts had a 15 to 35 per cent higher average grade of sclerosis than did the lighter ones. In general, heavier hearts had significantly higher grades of coronary atherosclerosis than did lighter hearts.

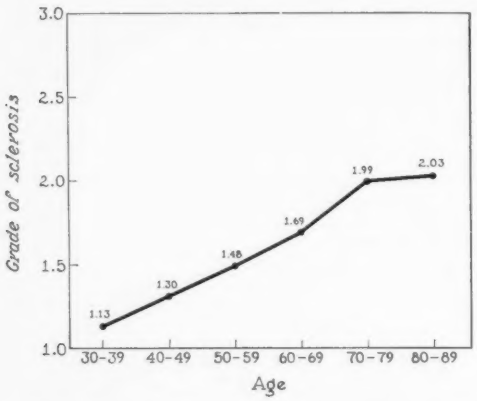

FIG. 5.—The average grade of coronary atherosclerosis by decades. For each heart the greatest sclerosis in each of the six major divisions was determined, and an average of the six values thus derived was obtained. For each decade these averages were totaled and divided by 100 to yield the average grade of sclerosis for that decade.

TABLE 1.—*Relation of Cardiac Weight to Coronary Sclerosis (All Hearts)*

Age, years	Hearts weighing 100-349 Gm.		Hearts weighing 350 Gm. or more		Per cent difference*
	Number	Sclerosis, grade	Number	Sclerosis, grade	
30-39	73	1.06	27	1.52	+43.4
40-49	75	1.22	25	1.54	+26.2
50-59	63	1.37	37	1.67	+21.9
60-69	49	1.57	51	1.81	+15.3
70-79	44	1.76	56	2.18	+23.9
80-89	46	1.83	54	2.20	+20.2
Totals.....	350		250		

* The percentage by which the average grade of sclerosis of the large hearts exceeded that of the small hearts.

Incidence of Clinical Coronary Disease

The 600 abstracted histories in the protocols were searched for a history of angina pectoris or evidence of myocardial infarction (table 3). The incidence of clinical diagnoses of coronary insufficiency paralleled to a remarkable degree the number of hearts with a *severe* degree of sclerosis. The 59 cases in which there was a clinical diagnosis of coronary disease represented 9.8 per cent of the total number of cases.

TABLE 2.—*Relation of Cardiac Weight to Coronary Sclerosis (All Diseased Hearts Except Those Associated With Hypertension Were Excluded If the Heart Weighed More Than 300 Gm.)*

Age, years	Hearts weighing 100-349 Gm.		Hearts weighing 350 Gm. or more		Per cent difference*
	Number	Sclerosis, grade	Number	Sclerosis, grade	
30-39	73	1.06	21	1.35	+27.4
40-49	74	1.22	20	1.65	+35.2
50-59	63	1.37	31	1.68	+22.6
60-69	49	1.57	50	1.81	+15.3
70-79	44	1.76	53	2.21	+25.6
80-89	45	1.85	54	2.20	+18.9
Totals.....	348		229		

* The percentage by which the average grade of sclerosis of the large hearts exceeded that of the small hearts.

TABLE 3.—*Age Distribution of Clinical Coronary Disease*

Age, years	Cases
30-39	1
40-49	3
50-59	3
60-69	14
70-79	20
80-89	18
Total.....	59 (9.8%)

Diabetes Mellitus and Coronary Atherosclerosis

The 600 protocols were reviewed to determine the number of cases of diabetes present

in each decade. Hearts from diabetics were then separated from those of nondiabetics. The average degree of sclerosis for each of the two groups was determined; this was higher in the diabetics than in the nondiabetics in every decade except the fourth and the ninth (table 4). In the ninth decade there was a slightly higher grade of sclerosis in the hearts of the nondiabetics; in the fourth decade there were no cases of diabetes to serve as a basis for comparison.

TABLE 4.—*Relation of Diabetes Mellitus to Coronary Sclerosis*

Age, years	Nondiabetics		Diabetics		Per cent difference*
	Number	Sclerosis, grade	Number	Sclerosis, grade	
30–39	100	1.13	—	—	—
40–49	98	1.11	2	1.50	+35.1
50–59	94	1.26	6	1.83	+45.2
60–69	95	1.45	5	1.84	+26.9
70–79	91	1.97	9	2.22	+12.7
80–89	97	2.03	3	1.93	−4.9

* The percentage by which the average grade of sclerosis of diabetics exceeded that of nondiabetics.

Relation of State of Nutrition at Death to Coronary Sclerosis

The cases were grouped according to whether the patient was underweight, of average weight or overweight, and the average grade of sclerosis was determined by decades for each of the three groups (table 5). The protocol description of the condition of bodily nutrition at the time of death was the criterion used to place each patient into one of the three named categories of the state of nutrition. The average grade of sclerosis in the underweight group was less than that in the average weight and overweight groups in each decade. The average grade of sclerosis in patients of average weight was essentially the same as that in persons who were overweight.

COMMENT

The literature indicates that coronary atherosclerosis increases steadily with age. White, Edwards and Dry found the hearts in men to have the highest degree of sclerosis in the sixth decade. The sclerosis decreases slightly in subsequent decades. In part this work has been confirmed by the data presented herein. In figures 3, 4 and 5 the severity of coronary sclerosis in women is shown to increase steadily with age from the fourth to the eighth decade, but there is a leveling off in the ninth decade. Figure 6 compares the manner in which atherosclerosis affected the coronary arteries in men and women; the curve for men is based on data presented by White, Edwards and Dry. The severity of the atherosclerosis was far greater in men than in women; nevertheless, after the seventh decade the average grade of sclerosis in men was only 13 to 17 per cent greater than in women. The curves for the two sexes are similar in that there is a leveling off in later decades. In men this occurs after the sixth decade; in women it occurs after the eighth decade.

What causes the marked difference in the

TABLE 5.—*Relation of State of Nutrition to Coronary Sclerosis*

Age, years	Underweight		Average weight		Overweight	
	Number	Sclerosis, grade	Number	Sclerosis, grade	Number	Sclerosis, grade
30–39	27	1.08	42	1.13	31	1.15
40–49	23	1.15	43	1.36	34	1.34
50–59	10	1.36	37	1.79	53	1.52
60–69	17	1.65	38	1.71	45	1.71
70–79	23	1.69	39	2.14	38	2.03
80–89	34	1.88	34	1.95	32	2.28
Totals	134	1.49	233	1.67	233	1.67

degree of atherosclerosis that occurs in men and women? Unfortunately, there is no ready explanation in the data presented herein. Some factor seems to have more influence than age. Figure 6 impresses one with the marked increase in atherosclerosis which occurs in the men from the fifth to the sixth decade. In women a comparable rise occurs between the seventh and the eighth decade. Some attempt should be made to determine if early menopause increases the prevalence of atherosclerosis in women.

Few studies have indicated the manner in which atherosclerosis affects the smaller

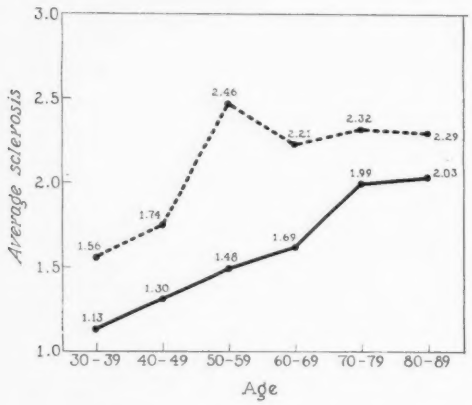

FIG. 6.—Comparison of the average grades of coronary atherosclerosis in men (dotted line) and women (solid line). The curve for men was constructed from data presented by White, Edwards and Dry.

branches of the coronary arteries. It has been held that the anterior descending branch of the left coronary artery is subject to a greater degree of atherosclerosis than are the other branches.[8] In our study the branches of the coronary arteries were involved by atherosclerosis in the following order of decreasing severity: left anterior descending, main right coronary, left circumflex, main left stem, posterior descending branch and marginal branch (figs. 1 and 3). This is in full agreement with the observations made in the parallel study of hearts in males. A severe degree of atherosclerosis (grade 3 or more) was present in the left coronary artery in a consistently greater number of hearts in each decade than in the right coronary. This tendency was more pronounced after the sixth decade. A severe degree of atherosclerosis was present in the right coronary artery in 3.2 per cent of the hearts when there was not a severe degree of atherosclerosis in the left coronary. White, Edwards and Dry found this relation in 11 per cent of hearts of men while Clawson[9] found such a relationship in less than 1 per cent of his series of 928 hearts from both men and women. The difference between right and left arteries is consistent. There is no acceptable explanation for this difference.

The 59 cases in which there was clinical evidence of coronary insufficiency in this series represented 9.8 per cent of the total number of subjects. This incidence compares with the estimates given by Master[10] for deaths from coronary disease for the entire population of the United States in 1942. He stated that disease of the coronary arteries accounted for 8.5 per cent of all deaths in this country. White, Edwards and Dry found that 11.5 per cent of the male patients had had clinical evidence of coronary insufficiency. Our series, then, is not unduly weighted with hearts which were known clinically to have disease of the coronary arteries.

The relation between hypertension and coronary atherosclerosis has been pointed out repeatedly.[8, 11, 12] In our series the only indication of hypertension consistently available was the cardiac weight. The fact that the average grade of coronary sclerosis in the heavier hearts was 15 to 43 per cent greater than that in the lighter hearts is in agreement with observations made in men.[5] The difference in men amounted to only 5 to 10 per cent. The clinical significance of a greater degree of sclerosis in hypertrophied hearts is apparent. A greater blood supply is necessary to support any cardiac hypertrophy. If there is impairment of the coronary circulation by atherosclerotic plaques in hypertrophied hearts the tendency will be to reduce blood flow and render such hearts more susceptible to failure. This obviously does not take the development of collateral circulation into consideration. Prinzmetal and Simkin[13] and others demonstrated that collateral circu-

lation is established by the coronary arteries in response to a decreased blood flow. It is difficult to know the functional effect of severe degrees of atherosclerosis on the myocardium when only morphologic data are at hand.

Since hypertrophied hearts do exhibit greater degrees of atherosclerosis in the coronary arteries than do hearts of normal size, the question is prompted: Is the hypertrophy due to hypertension or to the coronary insufficiency itself? Clawson[8] indicated that coronary atherosclerosis does not cause cardiac hypertrophy. This view is generally accepted. However, the cardiac hypertrophy which occurs when the left coronary artery has an anomalous origin from the pulmonary trunk[14] is strong evidence that coronary insufficiency can cause cardiac hypertrophy. Davis and Blumgart[15] observed a correlation between the degree of coronary atherosclerosis and cardiac hypertrophy when congestive failure had been present. When no congestive failure had been present there was little if any correlation between cardiac weight and degree of coronary sclerosis. No such comparisons were attempted in this study. Cardiac hypertrophy in a series such as this may indicate the presence of hypertension. It is possible that coronary insufficiency in itself may cause cardiac hypertrophy through the medium of causing myocardial insufficiency.[14] This matter must be kept in mind in evaluating the relation of coronary atherosclerosis to cardiac weight.

Of interest is the relation of coronary atherosclerosis to the state of nutrition. Our study showed that in each decade the underweight groups of subjects had less atherosclerosis than did the average weight or overweight groups. There was no difference between the average weight and the overweight groups, however. Wilens[16] has shown that terminal loss of weight decreases the number of fresh atheromatous deposits present in the aorta. This cannot be confirmed in this study because of lack of consistent knowledge of the state of nutrition for the entire group of patients prior to the terminal illness.

Summary

1. Six hundred hearts obtained from consecutive necropsies on women, 100 in each of the decades from 30 through 89 years of age, have been examined to determine the degree of atherosclerosis present in the coronary arteries.

2. The average degree of sclerosis, based on the maximal amount of sclerosis present in each heart, rose steadily from the fourth decade to the eighth decade and then tended to level off so that in the ninth decade there was approximately the same degree of coronary atherosclerosis as was present in the eighth decade.

3. The number of hearts with a severe degree of atherosclerosis rose steadily from 5 per cent in the fourth decade to 60 per cent in the eighth decade. Sixty per cent of the hearts in the ninth decade also had a severe degree of atherosclerosis.

4. Atherosclerosis was greatest in the anterior descending branch of the left coronary artery and next greatest in the main right coronary. The left circumflex, left main, posterior descending and marginal arteries followed in the order named.

5. Hearts exhibiting hypertrophy had a constantly greater degree of atherosclerosis than did nonhypertrophied hearts. This difference ranged from 15 to 43 per cent in general, and is striking because it appeared in all decades.

6. Coronary atherosclerosis was consistently less severe in the undernourished, but no differences were found in the average degrees of sclerosis for individuals of normal weight as compared to those who were overweight.

7. Diabetics had 12 to 45 per cent greater degrees of coronary atherosclerosis in the fifth to the eighth decades than did nondiabetics. In the ninth decade diabetics had 4.9 per cent less atherosclerosis than did nondiabetics. The total number of diabetics was only 25; it is felt that, in general, diabetics have a greater degree of atherosclerosis than do nondiabetics. The discrepancy in the ninth decade was not accounted for.

8. The pattern of development of atherosclerosis in the right coronary artery was similar to that in the left. There was, however, a greater average degree of atherosclerosis in the left coronary than in the right. In addition the left coronary artery showed a constantly greater degree of involvement by severe degrees of atherosclerosis than did the right coronary.

9. A comparison of our data with those compiled for a series of 600 hearts from men by White and associates is included.

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Penicillin Treatment of Patients with Cardiovascular Syphilis in Congestive Failure

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Congestive failure has been considered a relative contraindication to antisyphilitic therapy in cardiovascular syphilis since the arsphenamine era, when severe reactions were reported following administration of this vasculotoxic drug. After having observed no severe reactions to penicillin in a series of patients with cardiovascular syphilis, it was decided to administer the antibiotic as initial therapy for individuals in congestive failure. This report summarizes observations on twelve such patients. There were no severe reactions during the course of treatment in the entire group. Digitalis and other measures to restore compensation were used concomitantly with penicillin. All the patients were improved upon completion of therapy. Case histories of 2 patients who died two months after treatment, are given. The significance of observations on the entire group is discussed.

IN A RECENT communication, observations on 50 patients with penicillin-treated cardiovascular syphilis were presented.[1] Although the number of patients treated was relatively small, statistically speaking, it was felt that there was strong evidence that penicillin has no injurious effects as initial therapy in syphilis involving the cardiovascular system. Emboldened by this experience, we have now ventured one step further and have administered penicillin to 12 patients with cardiovascular syphilis in congestive failure. This report records our observations on these patients during and following treatment.

In the pre-penicillin era, cardiac failure was considered by many to be a contraindication to any antisyphilitic treatment with the exception of iodides.[2–4] Stokes and his associates[5] differed from the majority in that they felt that patients with cardiovascular syphilis in decompensation did better when weak spirillicidal agents such as mercury were administered concurrently with measures to restore compensation. The majority, however, believed that when decompensation was present the first essential was to relieve the congestive failure before administering more than the absolute minimum of antisyphilitic treatment. It was usually the practice to limit specific therapy to potassium iodide; in the presence of edema, one of the mercurial diuretics was given, principally for its diuretic and incidentally for its antisyphilitic effect. It was believed that some degree of cardiac reserve should be built up before bismuth or *small* dosages of an arsenical were even considered.[3] This seemingly ultraconservative approach was formulated because several severe and even fatal reactions had been known to occur following the administration of arsenicals[6–8]. Herrmann and Jamison[6] outlined a method of treatment for patients in congestive heart failure which emphasized again the conservative approach. Their opinion was based on a long and extensive experience which included the observation of "some fatalities" following the direct use of even small doses of neoarsphenamine in decompensated cardiovascular syphilis. Wilson and associates[8] observed electrocardiographic evidence of widespread myocardial disturbances directly following the introduction of arsenicals in the presence of congestive failure in patients with aortic syphilis.

Although there have been several reports on the treatment of cardiovascular syphilis with penicillin, a review of the literature revealed no reference to the treatment of decompensated cardiovascular syphilis with this antibiotic. Of the 12 patients in moderate to severe congestive heart failure whom we have treated

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TABLE 1.—*Pertinent Data on the Twelve Patients*

	Duration of Syphilis	Pre-Penicillin Treatment	STS Before Treatment	STS After Treatment	Amount and Dosage of Penicillin	Therapeutic Shock	Condition on Discharge	Present Condition
Case 1, G. N. (M), age 43, asymptomatic neurosyphilis, aortic regurgitation	Unknown—at least 27 years	Arsphenamine 12 injections 1922	Kline 256 units	20 mos. post-treatment Kline 2 units	Crystalline "G" 500 × 12 1,000 × 12 5,000 × 12 40,000 × 118	None	Improved	Improvement maintained 21 mos. post-treatment
Case 2, S. M. (M), age 49, aortic regurgitation, aneurysm innominate artery, hypertension, tabes dorsalis	30 years	4 arsphen. 1919; 6 mos. Maph. and Bi 1943; As and Bi 1945–46	Kolmer 44, Kahn 256 units	12 mos. post-treatment Kolmer 44, Kahn 2 units	Crystalline "G" 10,000 × 8 80,000 × 119 Total 9.6 mil. u.	None	Improved	Initial improvement for 15 mos., now more evidence of congestive failure
Case 3 P.I. (M), age 58, aortic regurgitation	Unknown	Hg. succinimide 6 injections; Potas. iodide gr. V t.i.d.; Bismuth 34 inj.; Mapharsen 14 inj.	Kline 256 units	—	Crystalline "G" 10.000 × 8 40,000 × 118 Total 4.8 mil. u.	None	Improved	Dead 57 days post-penicillin
Case 4, W. S. (M), age 39, aortic regurgitation	25 years	Potassium iodide; Bismuth 1940–41	Kline 256 units	—	Crystalline "G" 10,000 × 8 40,000 × 118 Total 4.8 mil. u.	None	Improved	Dead 66 days post-penicillin
Case 5, D. H. (M), age 69, aortic regurgitation, aneurysm ascending aorta	20 years	Bismuth weekly for 4 years	Kline less than 2 units	12 mos. post-treatment: negative	Crystalline "G" 500 × 20 10,000 × 7 40,000 × 118 Total 4.8 mil. u.	None	Improved	Improvement maintained 13 mos. post-treatment
Case 6, V.R. (M), age 59, aortic regurgitation	Unknown—at least 12 years	1937: 10 Neo 10 Bismuth 1946: 20 Maph. 1947: 26 Bismuth	Kline 128 units	11 mos. post-treatment: Kline 4 units	Crystalline "G" 10,000 × 8 40,000 × 118 Total 4.8 mil. u.	None	Improved	Improve. maintained 14 months post-penicillin
Case 7, S.R. (F), age 47, aortic regurgitation, hypertension	Unknown	None	Kline 128 units	13 mos. post-treatment: Kline 4 units	Crystalline "G" 10,000 × 8 40,000 × 118 Total 4.8 mil. u.	None	Improved	Improve. maintained 13 months post-penicillin
Case 8, V.S. (M), age 60, aortitis, hypertension	14 years	None	Doubtful	10 mos. post-treatment: negative	Crystalline "G" 10,000 × 8 40,000 × 118 Total 4.8 mil. u.	None	Improved	Improve. maintained 10 months post-treatment
Case 9, R.W. (M), age 67, aortic regurgitation	Probably 45 yrs?	Pot. iodide gtts. V daily in August 1948 for few days	Kline 256 units	4 mos. post-treatment: Kline 16 units	Crystalline "G" 5,000 × 8 10,000 × 4 40,000 × 18 Total 4.8 mil. u.	None	Improved	Improve. maintained 7½ mos. post-penicillin
Case 10, H.B. (M), age 50 aortic regurgitation	Unknown	Bismuth 40 injections	Kline less than 2 units	3 mos. post-treatment: Kline 8 units	Crystalline "G" 40,000 × 120 Total 4.8 mil. u.	Slight temperature elevation in 6 hours	Improved	Improve. maintained 7 mos. post-penicillin

Case 11, E.G. (M), age 67, aortic regurgitation, Ca of larynx	Unknown	None	Kahn 256 units	5 mos. post-treatment: Kahn 16 units	Crystalline "G" 1,000 × 10 5,000 × 6 40,000 × 119 Total 4.8 mil. u. Deep X-ray therapy to larynx	None	Improved	Improve. maintained 8 months post-penicillin
Case 12, L.H. (M), age 56, aortic regurgitation	Unknown—probably 30 years	40 Bismuth since 1943	Kolmer 44, Kahn 4 units	2 mos. post-treatment: Kolmer 44, Kahn 8 units	Crystalline "G" 40,000 × 120 Total 4.8 mil. u.	Temp. 100° 16 hours after first injection	Improved	Improve. maintained 2 months post-penicillin

TABLE 2.—*Status of Cardiovascular System Prior to Penicillin and at Time of Most Recent Examination*

	Before Penicillin			After Penicillin				
	Signs and Symptoms	Roentgen Findings	Electrocardiogram	Signs and Symptoms	Roentgen Findings	Electrocardiogram	Treatment with Penicillin	Treatment after Penicillin
Case 1, G.N. (M), age 43, asymptom. neurosyphilis; aortic regurg.	Progressive dyspnea and orthopnea 6 mos. Right pleural effusion. Liver moderately enlarged; moderate ankle edema; BP 156/60	Marked cardiac enlargement to left; aortic dilatation	Severe myocardial damage	21 months: improved, moderate dyspnea, slight ankle edema	Heart slightly smaller; aorta same. Moderate amt. fluid right lung base	Same	Digitalis; ammonium chloride; mercurial diuretic	Same
Case 2, S.M. (M), age 49, aortic regurgitation, aneurysm innominate artery; hypertension and tabes dorsalis	Ankle edema; severe dyspnea; severe upper substernal pain, especially nocturnal BP 196/120	Marked cardiac enlargement; aorta markedly dilated and dense; aneurysm innominate artery	Changes suggesting left ventricular hypertrophy.	18 months: initial improvement for about 15 months; now increasing signs congestive failure. BP 200/110	No change	Changes due to digitalis; otherwise same	Digitalis	Digitalis and mercurial diuretic (past 3 mos.)
Case 3, P.I. (M), age 58, aortic regurgitation	Severe angina pectoris and recurrent cardiac decompensation 2 yrs. Right pleural effusion; moderate pretibial edema. BP 160/50	Marked cardiac enlargement; aorta dense and dilated	Auricular fibrillation; severe myocardial abnormality	2 months: free of decompensation; no angina; then developed thrombophlebitis, pulmonary infarction; manic psychosis; died. (Details in paper)	No follow-up	No follow-up	Digitalis; ammonium chloride; mercurial diuretic	Same
Case 4, W.S. (M), age 39, aortic regurgitation	Angina pectoris 1 year; progressive dyspnea, orthopnea, nocturnal dyspnea; liver enlarged; rales both bases; moderate ankle edema. BP 150/40	Heart enlarged downwards and to left; T.D. 18 cms.; aorta diffusely dilated	Changes suggestive of left ventricular hypertrophy	Died suddenly at home 2 mos. post-penicillin treatment; cause unknown. (Details in paper)	No follow-up X-ray	No follow-up ECG	None	Digitalis, ammonium chloride, mercurial diuretic
Case 5, D.H. (M), age 69, aortic regurgitation (early); aneurysm ascending aorta	Dyspnea 4 yrs; progressive orthopnea; nocturnal dyspnea; rales both bases; moderate liver enlargement; marked ankle edema; BP 120/80	Heart only slightly enlarged; aorta dilated; aneurysm of ascending aorta	Severe myocardial abnormality; probable damage to anterior surface left ventricle	13 months: marked improvement; some dyspnea on exertion; no ankle edema	Heart normal in size; aorta unchanged	Same	Digitalis; ammonium chloride; mercurial diuretic	Same

TABLE 2—(*Continued*)

	Before Penicillin			After Penicillin				
	Signs and Symptoms	Roentgen Findings	Electrocardiogram	Signs and Symptoms	Roentgen Findings	Electrocardiogram	Treatment with Penicillin	Treatment after Penicillin
Case 6, V.R. (M), age 59, aortic regurgitation	Angina pectoris since 1937; severe dyspnea and occasional orthopnea; marked pretibial edema; BP 174/60	Marked cardiac enlargement, esp. left ventricular; aorta diffusely dilated	Slight depression RS-T segments in most leads	14 months: no congestive failure; no dyspnea; no angina; BP 142/60	Heart slightly smaller; T.D. 16.9 cm. compared with 18.5 cm.	Same except for digitalis effects	Digitalis; mercurial diuretic	Digitalis
Case 7, S.R. (F), age 47, aortic regurgitation, hypertension	Progressive dyspnea 3 years; ankle edema 6 mos. Admitted in acute cardiac decompensation; rales both bases; liver mod. enlarged; marked pretibial edema. BP 160/70	Marked enlargement; aorta moderately dilated	Changes of type seen in left ventricular hypertrophy	13 months: marked improvement; no evidence of congestive failure. BP 170/80	Heart smaller; top normal size, configuration of left ventricular hypertrophy	Digitalis effects; otherwise unchanged	Digitalis; mercurial diuretic	Digitalis, ammonium chloride, mercurial diuretic
Case 8, V.S. (M), age 60. aortitis, hypertension	Progressive dyspnea; rales both bases. Marked ankle edema; relieved by digitalis and mercurials. Severe substernal pain nightly; relieved only by opiates. BP 190/110	Heart markedly enlarged; aorta marked generalized dilatation and elongation	Changes suggesting left ventricular hypertrophy; also digitalis effects	10 months: marked improvement; oppression in upper chest relieved second day of treatment. No recurrence	No change	No change	Digitalis; mercurial diuretic	Same
Case 9, R.W. (M), age 67, aortic regurgitation	Progressive dyspnea for 2 years; orthopnea; marked ankle edema; liver enlarged 5 cm. below costal margin; right pleural effusion. BP 160/30	Marked cardiac enlargement especially to left; aorta markedly and uniformly dilated	Auricular fibrillation; changes of type seen in left ventricular hypertrophy	7 months: marked improvement; slight dyspnea; no bilateral ankle edema	Heart slightly smaller	Unchanged	Digitalis; ammonium chloride; mercurial diuretic	Same
Case 10, H.B. (M), age 50, aortic regurgitation	Angina pectoris, progressive ankle edema and dyspnea; orthopnea 45 years; liver 3 cms. below costal margin. BP 160/70	Marked cardiac enlargement; aorta dilated and dense	Signs suggesting left ventricular hypertrophy. Minor grade heart block	7 months: much improved, no evidence of congestive failure; no angina	No change	No change	Digitalis; mercurial diuretic	Same
Case 11, E.G. (M), age 67, aortic regurgitation, Ca of larynx	Ankle edema; severe dyspnea; rales in both bases; liver enlargement. BP 160/50	Marked cardiac enlargement; aorta dilated	Numerous extrasystoles; left ventricular hypertrophy	8 months: no rales in bases. Slight dyspnea on exertion	No change	No change	Digitalis; Salyrgan; oxygen; aminophyllin	Digitalis and mercurial diuretic
Case 12, L.H. (M), age 56, aortic regurgitation	Ankle edema; orthopnea; moist rales throughout chest liver enlargement. BP 160/60	Marked cardiac enlargement and diffuse dilatation of the aorta	Signs indicative left ventricular hypertrophy	2 months: marked improvement; moderate dyspnea on exertion; no nocturnal dyspnea	No change	No change	Digitalis; Salyrgan, ammonium chloride; Dilaudid	Digitalis and Salyrgan

with penicillin, none was prepared with less potent spirocheticidal agents. All were closely observed in the hospital under complete bed rest and low-salt diet. Digitalis, ammonium chloride and mercurial diuretics were started at the same time as the penicillin in all but one patient. The initial penicillin dosage ranged from 500 to 50,000 units every two hours and the total dosage from 4.8 to 9.6 million units of crystalline penicillin G. Examinations which included electrocardiograms and fluoroscopic studies were made before and at varying periods after treatment. In addition, electrocardiograms were made at approximately three-day intervals during the period of penicillin treatment. The pertinent facts concerning each patient are outlined in tables 1 and 2.

Results

Each of the 12 patients in cardiac failure tolerated his course of penicillin without serious untoward immediate reaction. The only suggestion of therapeutic shock was a slight febrile reaction in 2 patients, H. B., case 10, starting six hours after initiation of penicillin therapy, and L. H., case 12, starting sixteen hours after the first injection. In no instance was it considered necessary to interrupt the treatment schedule. None of the patients showed increasing evidence of congestive failure, but on the contrary, all seemed to be symptomatically improved within forty-eight to seventy-two hours after initiation of treatment. Electrocardiographic studies revealed T-wave abnormalities and other changes which could be attributed to digitalis, but in no instance was there evidence of intraventricular conduction defects. All of the patients were able to leave the hospital immediately after completion of penicillin therapy (usually in ten to twelve days) in an improved state. Maintenance dosages of digitalis were prescribed and 7 were continued on mercurial diuretics. The post-treatment follow-up now ranges from two to twenty-one months.

Two of our patients died two months following completion of penicillin.

The first patient, a 58 year old white man (Case 3) had experienced angina and several episodes of severe cardiac failure over a period of fifteen months. Advanced aortic insufficiency of syphilitic etiology was discovered in December 1946 at the time of his first admission to the hospital in acute left ventricular failure. There was no history of previous antisyphilitic treatment. His reaction to the blood serologic test for syphilis was strongly positive and the spinal fluid examination was negative.

In January 1948 he was admitted to the Institute for the Study of Venereal Disease in severe decompensation. Treatment consisted of a total of 4.8 million units of penicillin (40,000 units every two hours), digitalis, ammonium chloride and Salyrgan. He was much improved symptomatically at the time penicillin therapy was completed and was discharged on a maintenance dose of digitalis and a mercurial diuretic. Following his return home, however, his course was gradually downhill; he became increasingly weak, and developed nausea and vomiting. On February 19, 1948 (just one month after completion of penicillin) he was admitted to the medical ward "in a shocklike state." He complained of severe pains in his calves and was experiencing hemoptysis. He was in acute left ventricular failure, and had a right pleural effusion. X-ray study of the chest revealed irregular densities in both lung fields believed to be due to pneumonia or infarcts. During his period of hospitalization from February 19 to March 12, 1948, he became manic and was to have been transferred to the psychiatric ward of a municipal hospital with the diagnoses of acute manic psychosis, thrombophlebitis, and pulmonary infarct, in addition to the cardiovascular disease previously described. It appears that his family took him home in preference to admitting him to the psychiatric ward, and he died one week later. No autopsy was performed.

The second patient, who died two months following penicillin therapy, was a 39 year old Negro who had acquired syphilis about twenty-three years before. He had been rejected for military service in 1940 because of "heart disease" and a positive serologic test for syphilis, and was referred to a public health clinic for treatment. This consisted of weekly intramuscular injections (? bismuth) and "drops" (? potassium iodide) for one year. Following this, he allowed his treatment to lapse. He gradually began to experience dyspnea on exertion and weakness until about a year prior to his admission, when he developed increasing symptoms and signs of cardiac failure (paroxysmal nocturnal dyspnea, orthopnea, ankle edema, precordial pain). Examination at the time of admission to the hospital revealed marked cardiac enlargement (transverse diameter 18.0 cm.), a "to-and-fro" aortic murmur, blood pressure 150/40, 2-plus ankle edema, and occasional basal râles. Signs of congestive failure diminished on bed rest. His serologic test for syphilis was strongly positive; the cerebrospinal fluid was negative. He was given penicillin without any supportive cardiac therapy (10,000 units every two hours for eight doses, and then 40,000 units every two hours to a total of 4.8

million units). There was no evidence of a febrile or other untoward reaction during the course of treatment. He was discharged symptomatically improved but returned to the cardiac clinic a month later with an upper respiratory infection and with a recurrence of symptoms and signs of moderate cardiac failure. A digitalis glycoside was prescribed. He seemed to be holding his own on a regimen which included digitalis, ammonium chloride and mercurial diuretics until he "suddenly became very ill" at home, sixty-six days after completion of penicillin therapy, and was taken to a municipal hospital where he was pronounced dead on arrival. Autopsy was not obtained.

Discussion

We do not have sufficient evidence as yet to show that penicillin alters the course or prognosis of decompensated cardiovascular syphilis, but it seems significant that the patients in this study were apparently able to tolerate large doses of this powerful spirillicidal agent, even though they were in acute congestive heart failure when treatment was started.

It has been shown that penicillin is well tolerated by patients with late cardiovascular syphilis[1, 9, 10] In the paper previously alluded to[1] we reported our observations on 50 cases of late cardiovascular syphilis treated with penicillin. Physical examinations and electrocardiographic studies made before, during and within the available period of observation after treatment failed to disclose any deleterious effects upon the cardiovascular system during or following the use of penicillin.

The apparent lack of immediate unfavorable effects when penicillin is given to patients with cardiovascular syphilis and congestive failure is significant, for it is this type of patient who received little or no antisyphilitic treatment before the penicillin era. It is not unlikely that some of the arsphenamine fatalities which were attributed to the Jarisch-Herxheimer reaction were due to the toxic effects of the drug on an already damaged cardiovascular apparatus. Wilson and associates[8] observed the development of an abnormal idioventricular rhythm following the administration of 0.2 Gm. of arsphenamine to a syphilitic patient who showed right bundle branch block in the electrocardiogram; death occurred a few days later. Two other patients with syphilitic aortitis, with practically normal electrocardiograms, developed diphasic QRS complexes, suggesting incomplete bundle branch block, following intensive arsphenamine therapy. We have treated with penicillin over 100 patients, including the 12 in cardiac failure (and 3 with healed myocardial infarctions), and although transient T-wave changes were noted, conduction defects, except those due to digitalis, were absent.

If the Jarisch-Herxheimer reaction is accepted as the cause of most immediate untoward reactions in patients with cardiovascular syphilis treated with arsphenamine, how then can we reconcile the apparent lack of reaction in the same type of patient treated with penicillin? It might be argued that the difference in mode of action of the two drugs on the spirochete could of itself account for this seemingly marked difference in toxicity. However, one has merely to note the frequent occurrence of Herxheimer reactions in patients with early syphilis treated with penicillin, as compared with the arsenicals, to realize that penicillin is more likely than arsphenamine to produce this type of reaction. A tenable hypothesis is that the difference lies in the inherent toxicity of arsphenamine for the damaged cardiovascular system.

What about the phenomenon of therapeutic paradox? We can state with some certainty, that if it occurs at all, it is apparently uncommon in penicillin-treated cardiovascular syphilis. It is not possible to determine clinically whether progression of the process in a particular patient is the result of his disease or is due to too rapid healing with scar formation and contracture in a vital structure. If aortic regurgitation happens to occur following treatment of syphilitic aortitis, it seems as reasonable to assume that the process has progressed to involve the aortic ring and valves as it is to attribute it to therapeutic paradox. Such a sequence sometimes occurs quite rapidly without any treatment at all; the course of syphilitic heart disease is often unpredictable, as has been shown by Reader and associates.[11] It is to be expected that some patients may decline coincidentally with or after treatment. Of course, this is speculation which will not be substantiated or refuted

until many more patients have been treated and autopsies obtained on those who die following treatment.

It is not possible at the present time to predict what the long-term effect of immediate penicillin treatment upon decompensated cardiovascular syphilis will be.

Summary and Conclusions

1. Twelve patients with syphilitic cardiovascular disease and congestive failure were treated with penicillin.

2. No untoward reactions, except for slight early febrile reactions in 2 patients, were observed during treatment. The total dosage varied from 4,800,000 to 9,600,000 units. Two patients were started on 500 unit doses; 8 patients on 10,000 units; 2 patients received large initial doses—40,000 units every three hours. The duration of treatment was twelve to fifteen days.

3. There were two deaths, the case histories of which are presented. Unfortunately, autopsies were not performed in either patient.

4. All patients were improved on leaving the hospital. We cannot yet state how much of this improvement was due to penicillin; longer and more extensive experience is needed. It is also impossible to predict whether or not therapeutic paradox may not ensue and a new decompensation or death be precipitated more readily because of the use of penicillin.

5. It is our present impression that patients with syphilitic cardiovascular disease in cardiac failure react better to the combined treatment with penicillin than those who receive only treatment for congestive failure. We are encouraged by our observations to date. If penicillin can convert an active process in the aorta to an inactive one, it seems reasonable to assume that life can be prolonged in patients in whom the process is not too far advanced.

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The Effect of Epinephrine on the Myocardium of the Embryonic Chick

By ALEXANDER BARRY, PH.D.

The myocardium of the embryonic chick heart, before it has been innervated, responds to concentrations of epinephrine as dilute as 1 part in 20,000,000 by an abrupt acceleration in its inherent rate of pulsation. The more slowly the heart beats initially, the more marked is the accelerating effect of epinephrine. Usually the initial acceleration is followed by a period during which the heart slows to a rate intermediate between the initial and the maximal. This deceleration is not due to a decrease in the stimulating effect of the drug applied.

THE FOLLOWING report is concerned with the moot question as to whether or not the sympathomimetic substance, epinephrine, is effective in accelerating the rate of pulsation of the myocardium of the chick embryo prior to the establishment of its innervation (i.e., before the fifth day of incubation, according to His[5]).

In 1927, Fujii[3] reported that in chick embryos up to the third day of incubation, adrenalin had no effect on the rate of cardiac pulsation except in "large doses," and that the first characteristic response was obtained in chicks during the fourth day of incubation. In 1931, Nordmann and Rüther[9] stated that the rate of pulsation of the pacemaking centers in explants of the myocardium of chick embryos of various ages was not influenced by adrenalin. In the same year, Markowitz[8] examined the effect of epinephrine on explanted cardiac tissue from chick embryos. This work assumed that no change in rate less than 25 per cent was significant. Using this criterion, it was found that out of 38 tested, ten explants from chick embryos of 2 to 3 days of age reacted to epinephrine; and that explants from older embryos yielded a higher percentage of positive reactions. All explants showed "typical physiologic reactions" when they were taken from embryos older than 6 days of incubation. It was assumed from the foregoing observation that a substance within the myocardium was responsible for the "typical response" of cardiac tissue to epinephrine. This substance appeared to be absent from most 72-hour embryos, but was present in increasing concentrations in older embryos.

Two years later Hsu[6] reported that epinephrine was effective in accelerating the rate of intact embryonic chick hearts between the ages of 53 and 103 hours, and of fragments from hearts between the ages of 37 and 480 hours of incubation. The greatest acceleration obtained for any fragment of the heart was 115 per cent, and Hsu stated that there was a great variation in the sensitivity of the individual hearts which was not correlated with differences in age, concentration of drug, or other known environmental factors. It was because of the disagreements in the above reports, that the present investigation was undertaken.

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METHODS

Chick embryos of Rhode Island Red stock were removed from the egg and placed in sugar-free oxygenated Ringer-Locke solution. The body of the embryo was transsected immediately cephalic to the aortic arches and caudal to the sinus venosus. The parietal pericardium and attached body wall were removed to allow free access of the oxygenated saline to the epi-myocardium. The resulting block of tissue was placed in 20 cc. of oxygenated Ringer-Locke solution at 38 C. The desired segment of the cardiac tube was excised and mounted in the recording apparatus. When the rate of the entire heart or of the sinus segment was studied, the caudal end of the heart was left attached in its normal relationship to the axial portion of the body.

The recording apparatus, illustrated in figure 1, can for brevity be called a micromyograph. It consists of a small glass hook attached to an adjustable glass arm, which can be raised or lowered by means of a fine screw adjustment. The piece of tissue to be examined is impaled by one end to this hook. The other end of the segment of tissue is attached to the hooked end of a thin glass filament. The upper end

of this filament hooks over a short side-arm which is so cemented to a rubber band that a vertical movement imparted to it will twist the band. A mirror 0.015 by 0.030 inches in size (GE #NP-61770) is fixed to the rubber band so that it deflects a beam of light as the rubber band is twisted. The movements of this optical lever are recorded on the moving film of a slit camera. The rate of pulsation of the heart segment can thus be determined by measuring the distance between deflections on the photographic record. When such precision is not needed, the rate of pulsation is measured with a stopwatch.

It was found that the rate of pulsation of the heart segment was slightly influenced temporarily by sudden increases in the tension to which it was subjected. Thus, if the saline medium surrounding the tissue was unduly agitated, the resulting eddy currents tended to stretch the tissue, and its rate of pulsation increased slightly. In no case was this increase in rate found to exceed 10 per cent. Nevertheless, to control this slight source of variability, after a given segment of heart was placed in the apparatus it was allowed to remain untouched until its rate of pulsation reached a steady state (usually about ten minutes). Then, while its pulsations were being photographically recorded, 0.2 cc. of Ringer-Locke

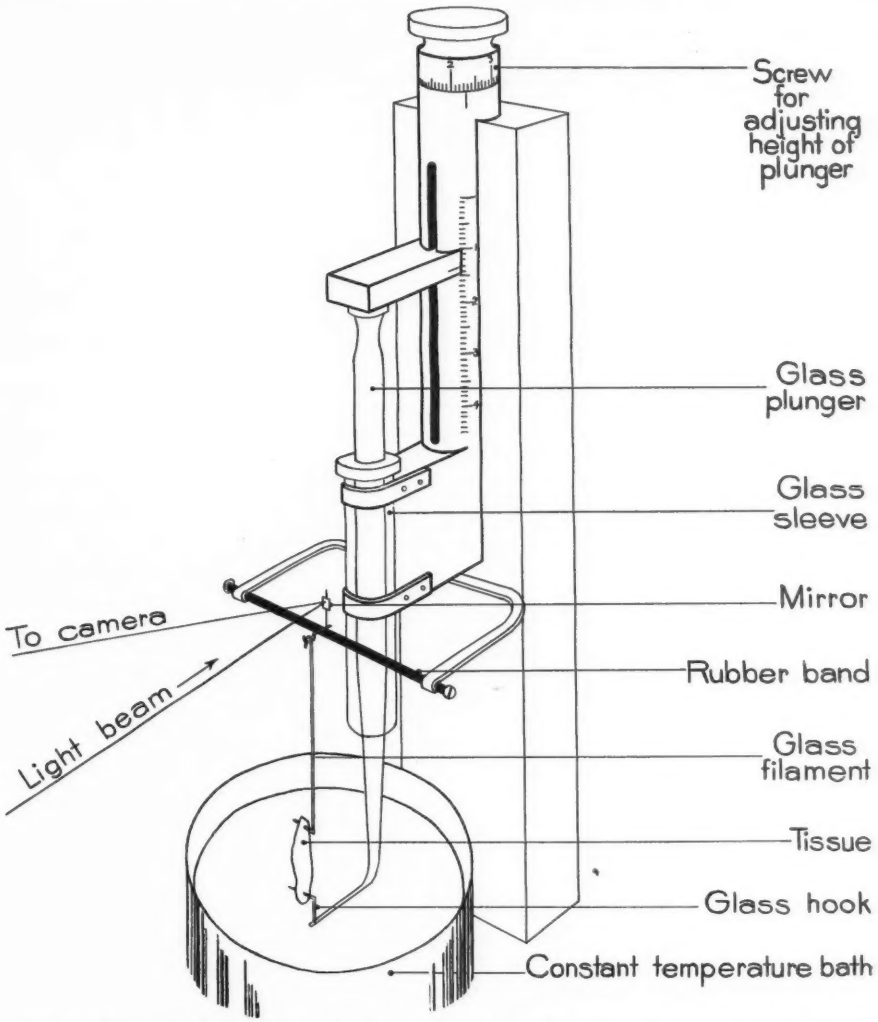

FIG. 1.—Diagram showing the construction of the micromyograph used to record length changes of small segments of embryonic myocardium.

solution was added to the saline bath. The small resultant alterations in rate, if present, served as a control for evaluating the effect of epinephrine which was subsequently added in precisely the same manner.

A, 0.2 cc. of Ringer-Locke solution was added to the saline bath. The resultant increase in rate was minimal. After one minute's pause, 0.2 cc. of epinephrine at a concentration of 1

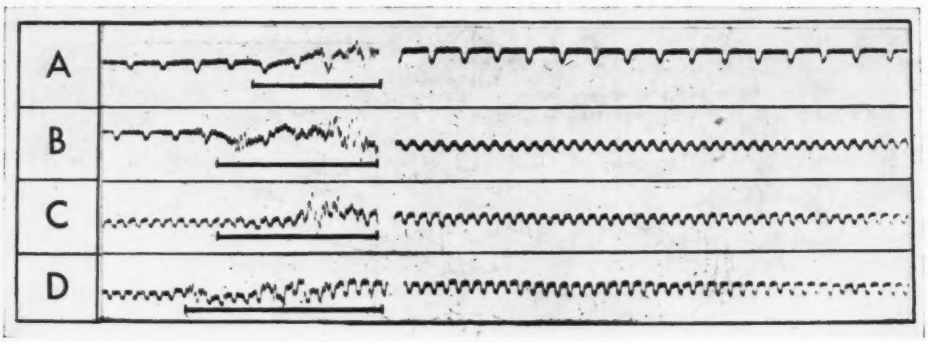

FIG. 2.—Photographic recordings of the pulsations of the ventriculoconus segment of the heart of a 70 hour chick, showing the effect of Ringer-Locke solution and epinephrine on its rate of pulsation. *A* shows the absence of acceleration when Ringer-Locke solution was added. *B* shows the acceleration when epinephrine was added to make a concentration of 1 part in 20,000,000. *C* shows the lack of additional acceleration when the concentration of epinephrine was increased to 1 part in 10,000,000. *D* shows lack of additional acceleration when the concentration of epinephrine was increased to 1 part in 500,000. The bars beneath the records indicate the time the substances were added. The irregularities over each bar are due to tension changes caused by eddy currents in the fluid set up by the addition of the drug. The interruption of each record shows the time the addition was completed.

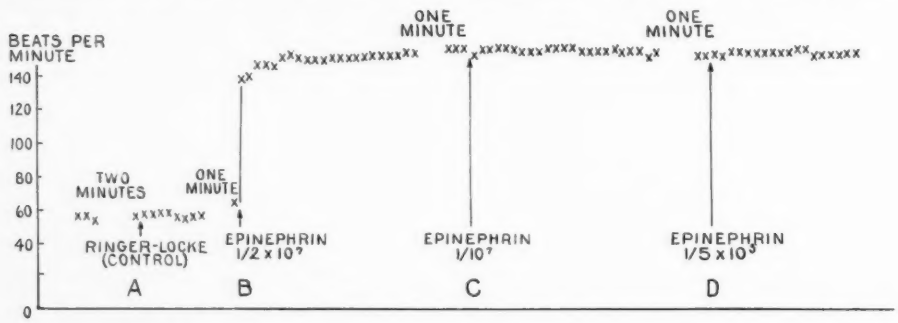

FIG. 3.—Graph showing the effect of Ringer-Locke solution and successive additions of epinephrine on the rate of the same heart segment as in Fig. 2. The rate is indicated in beats per minute on the ordinate scale.

RESULTS

The photographic records from a typical experiment are shown in figure 2. Figure 3 presents the results from the same experiment, plotted as rate against time. The ventriculoconus segment of the heart of a 70-hour chick was placed in the micromyograph. After ten minutes its rate of pulsation was reasonably steady at about 55 beats per minute. At point

part in 200,000 was added (point *B*). This resulted in a concentration of 1 part in 20,000,000 in the saline solution surrounding the cardiac tissue. As can be seen from figure 2, the pulsation frequency had increased to 150 beats per minute by the time the last of the dose of epinephrine had been added (i.e., within five seconds). The pulsations were recorded for a full minute. After one minute's pause the same

dosage of epinephrine was repeated, bringing its concentration to 1 part in 10,000,000 (point *C*). There was no further appreciable increase in rate. After another minute's pause more epinephrine was added, bringing its concentration to 1 part in 500,000 (point *D*). Again, this higher concentration caused no further increase in the pulsation frequency of the heart segment.

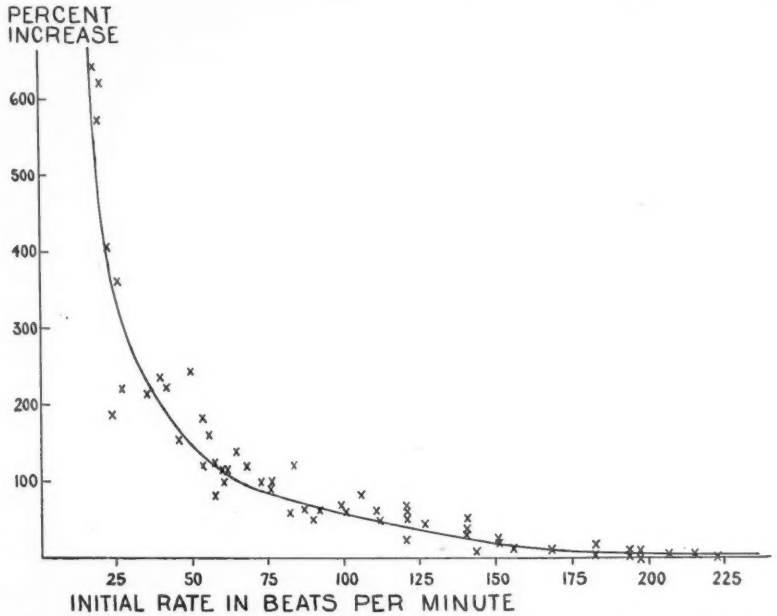

FIG. 4.—Graph showing the effect of epinephrine on the pulsation rate of segments of embryonic chick myocardium. The ordinate shows the increase in rate as per cent of the initial rate, which is plotted in beats per minute along the abscissa.

From a series of such experiments it was found that concentrations of epinephrine varying between 1 part in 20,000,000 and 1 part in 20,000 would produce maximal effects on the rate of beating of the cardiac segments. However, these should not be considered limiting values since no attempt was made to establish threshold concentrations.

Segments of various regions of the heart at different ages were tested as described above (figs. 2 and 3). It was found that, under the experimental conditions described, all but a few segments from the sinus venosus of hearts at any stage after this chamber had been formed beat consistantly faster than 160 beats per minute before the addition of epinephrine. Segments from the atria, ventricles and conus showed the expected lower inherent rate of pulsation.[2,7]

The results from tests on 55 hearts and segments from hearts of chick embryos of between 40 and 170 hours of incubation are shown in fig. 4. It can be seen that the degree of maximum acceleration depends upon the initial rate. If the tissue was beating at a rate faster than 180 beats a minute, the acceleration induced by epinephrine was less than 10 per cent, and was not considered significant. Tissues with an initial rate slower than 180 beats per minute were accelerated by the addition of the drug; the more slowly the tissue beat initially, the more marked was its acceleration.

In some cases the initial acceleration induced by epinephrine was followed by a more gradual deceleration which usually reached a plateau at a rate between the initial and maximum rates of pulsation. There was a general trend among all the cardiac segments tested for the more slowly pulsating segments to show

this secondary phase of deceleration more markedly than those segments whose initial rate was more rapid. In other words, segments with a lower inherent rhythmicity tended to respond to epinephrine by a more transient phase of acceleration. However, there were many exceptions to this general rule, which could not be correlated with any of the variables measured, such as age, initial rate, and location within the heart.

It was not thought that this deceleration was due to a decrease in the concentration of epinephrine surrounding the tissue to a level giving less than the maximal response, since in most tests a concentration of epinephrine of 1 part in 100,000 was employed. At this strength, 99 per cent of the epinephrine could be destroyed or inactivated, and still leave a concentration (1 part in 10,000,000) which had been previously shown to elicit a maximal response from the cardiac tissue. There was no indication that under the conditions of the experiment any significant degree of oxidation of the drug took place. Nevertheless, a test was made to determine whether the epinephrine might have been inactivated in some unsuspected manner during the period of observation. The heart from a chick embryo of 72 hours' incubation age was tested as described above with a concentration of 1/100,000 epinephrine. This heart showed the usual acceleration, increasing its rate of pulsation by 50 per cent. After ten minutes the heart was discarded, but the solution was saved and kept at room temperature. A second heart of the same age as the first was mounted for testing in 20 cc. of Ringer-Locke's solution. After it had attained a steady rate of pulsation at 73 beats per minute, 20 cc. of the 1/100,000 solution used in the previous experiment was added. The rate of pulsation promptly accelerated to 118 beats per minute (62 per cent). Thus it is evident that the solution of epinephrine at the end of the first experiment was sufficiently effective so that even when diluted to half strength, it still elicited a typical response from a second heart. This seemed to give adequate evidence that the deceleration following the initial acceleration of the pulsation rate was not due to a decrease in the concentration of the epinephrine in the environment of the heart segment. Neither was it due to alterations in temperature nor in tension.

Discussion

The sinus venosus of the embryonic chick heart has been formed and has assumed its role of pacemaker at about 22 to 25 somites (46 to 48th hour of incubation, according to the age scale of Patten[10]). At this time the rate of the excised heart or of the sinus venosus is about 160 to 180 beats per minute at 38 C.[1] Thus it might be predicted that the rates of entire hearts, or segments of the heart whose pace is set by the sinus venosus, (i.e. from embryos older than 46 to 48 hours, incubation age), will not be accelerated by epinephrine. This was found to be the case. However, in a few instances it was found that a segment of the sino-atrial region of the heart pulsated initially at a rate less than 160 beats per minute. In these cases epinephrine was effective in accelerating its rate of pulsation. It is possible that in these segments the pacemaker was actually atrial in position, either because the sinus was not pulsating, or because there was a sino-atrial conduction block. Either of these hypotheses would account for the unexpectedly low inherent rate of pulsation of the segment.

It is interesting to note that the response of the embryonic myocardium of the chick to epinephrine is essentially the same as that of the ventricle of the adult human heart in cases of complete heart block. Concerning this condition, Goodman and Gilman[4] state that there is a direct correspondence between the drug induced acceleration of the ventricle and the initial rate, such that the slower the original rate, the more pronounced is the accelerating effect of epinephrine. When the initial rate is high, epinephrine has little further action on it. This behavior is not found in the case of the atrial contractions of a heart in complete heart block. It is perhaps significant that the rate of the atrial contractions is set by the rate of the sino-atrial node, a region morphologically and physiologically distinct from the rest of the cardiac muscle, and derived embryologically

from the right horn of the sinus venosus. This region, moreover, even in a case of complete heart block, would still be under the influence of nervous regulation.

Thus the myocardium, even during its first hours of pulsation, long before it receives its autonomic innervation, is capable of responding to this sympathomimetic drug in a manner quite comparable to that of the adult myocardium. It seems unnecessary to assume any qualitative changes in the myocardium in this respect between the time of its first pulsation and the time of its innervation. The characteristic myocardial response to epinephrine is present in essentially its adult condition in the epimyocardium of the young embryo during its prenervous phase of pulsation.

It is obvious that the conclusions to be drawn from this study with regard to the effectiveness of epinephrine in stimulating the embryonic myocardium differ markedly from the results of the work of Fujii[3], Markowitz[8] and Nordmann and Rüther[9], and agree, at least qualitatively, with those obtained by Hsu[6]. The work of Nordmann and Rüther and part of that of Markowitz was done on explanted fragments of embryonic myocardium in tissue culture. The present tests were carried out in sugar-free Ringer-Locke solution to avoid the unmeasurable effects of the tissue extracts used in culture media, and to eliminate the necessity of evaluating the effects of possible metabolic changes which might be undergone by the myocardial cells as they proliferate in tissue culture.

Hsu determined the effect of epinephrine by transferring the cardiac tissue to be observed between the test concentration of the drug and a control saline environment. It was to avoid this mechanical stimulation as a possible source of error that the tissues in the present experiments were subjected to as little mechanical disturbance as possible during the tests. The photographic recording of the contractions of the cardiac segments in the present series of experiments also allowed one to measure the time between each pulsation of the tissue before, during, and after the addition of the epinephrine, thus allowing one to observe and measure even a transitory phase of acceleration, which might otherwise have been overlooked.

Summary

Epinephrine in concentrations as dilute as 1 part in 10,000,000 in Ringer-Locke's solution was applied to entire hearts and segments of hearts of chick embryos between the ages of 40 hours and 7 days of incubation. It was found that epinephrine caused an abrupt acceleration of slowly beating tissues, reaching a maximum rate within a few beats. Usually within thirty seconds this rapid rate began to decrease until in ten to fifteen minutes it had leveled off to a rate intermediate between the initial and the maximal rate. This deceleration was not due to a decrease in the stimulating effect of the drug applied.

The degree of the first acceleration depended upon the initial rate of pulsation before the drug was added. The slower the initial rate, the greater was the per cent acceleration. When the initial rate was faster than 180 beats per minute, the addition of epinephrine produced no significant acceleration. This relationship held true for entire hearts and segments of hearts regardless of the age of the embryo from which they were taken.

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The Editorial Board and the Publisher of Circulation

ANNOUNCE

the inauguration of a Section on

CLINICAL PROGRESS

to appear monthly, beginning in the Fall of 1950

DR. HERRMAN L. BLUMGART

will serve as Editor of this Section

Representative topics planned for this Section are listed on the reverse side of the page

The following topics are among those planned for presentation in forthcoming issues in Clinical Progress:

THE MODERN TREATMENT OF CORONARY THROMBOSIS WITH MYOCARDIAL INFARCTION

THE TREATMENT OF HYPERTENSION

ANTICOAGULANTS IN PERIPHERAL VASCULAR DISEASE

CHOLESTEROL AND THE LIPIDS IN ARTERIOSCLEROSIS

EMERGENCY TREATMENT OF ACUTE HEART FAILURE

CORTISONE AND ACTH IN RHEUMATIC FEVER

THE ACTION AND USES OF THE MERCURIAL DIURETICS

THE CIRCULATORY MANIFESTATIONS OF EMOTION

ANTIBIOTICS IN THE PREVENTION OF HEART DISEASE

ABSTRACTS

BACTERIAL ENDOCARDITIS

Mouquin, M., Coujard, R., Macrez, C., and Ascoli, P.: Recurrences of Osler's Disease. Arch. d. mal. du coeur **42:** 838 (Aug.), 1949.

The authors present 6 cases of subacute bacterial endocarditis healed by penicillin. In 5 of the cases a recurrence of the disease was observed after 2 to 3 years; in one case two relapses occurred after 8 and 5 months, respectively. All responded well to new and massive treatment (1 to 10 million units of penicillin per day). One patient died on the thirtieth day of treatment of a cerebral hemorrhage. Histological examination of the heart showed clearly the recent inflammatory lesions of the endocardium superimposed on fibrous and sclerotic changes; this indicated healing of the primary process. The authors consider the possibility of an increased susceptibility of a healed subacute bacterial endocarditis to reinfection, which would represent an indication for prophylactic treatment.

PICK

BLOOD COAGULATION

Moolten, S. E., Vroman, L., and Vroman, G. M. S.: Adhesiveness of Blood Platelets in Thromboembolism and Hemorrhagic Disorders. II. Diagnostic Significance of Platelet Adhesiveness. Am. J. Clin. Path. **19:** 814 (Sept.), 1949.

Measurement of platelet adhesiveness by the glass-wool filter may aid in diagnosis and interpretation of hemorrhagic and thrombotic disease. In thrombocytopenic purpura extremely low adhesiveness is suggestive of hypersplenism; normal or elevated adhesiveness implies primary marrow disease (leukemia, etc.) In hemophilia the adhesiveness is normal or elevated. Moderate hypersplenism, revealed by reduced platelet adhesiveness, is common in nonsuppurative systemic infections, hyperthyroidism and late pregnancy.

Hyperadhesiveness, with or without a rise in total platelet count, accompanies cellular destruction anywhere in the body. It occurs regularly during uncomplicated convalescence from operation or accidental trauma. It is marked in ischemic necrosis. Continuous hyperadhesiveness is common in cancer, blood dyscrasias (polycythemia vera and idiopathic thrombocythemia) or as an independent entity (essential thrombophilia).

Marked platelet adhesiveness predisposes to thrombosis. Rapid fall in platelet count, particularly adhesive platelets, warns of developing thrombosis, usually massive, as in the ventricle following myocardial infarction. In extreme cases, purpura may occur because the blood is depleted of adhesive platelets.

Thrombocytosin, a fat-soluble agent stored in adipose tissue and abundant in egg yolk, increases platelet count and adhesiveness. It is mobilized during tissue breakdown and it is also absorbed with the diet. Thrombocytopen formed by the spleen is its antagonist. Both agents affect platelet count and adhesiveness significantly in man and may have therapeutic application to purpura and tendencies to thrombosis. The suppression of thrombin formation by heparin, which retards platelet lysis, also reduces platelet adhesiveness; the total platelet count, however, is maintained or slightly raised. Dicumarol has much less effect on platelet adhesiveness.

LECKS

Sternberger, L. A.: Dicumarol Therapy Controlled by the Stabilized Thrombin Method for the Determination of Prothrombin. Blood **4:** 1131 (Oct.), 1949.

The author proposes a stabilized thrombin two-stage method which he states is independent of any of the variable factors in the one-stage method of Quick and, in addition, gives results in absolute units. It is based upon his observation that alcohol suppresses the antithrombic activity of plasma, so that it is possible to keep constant the amount of thrombin obtained after quantitatively converting prothrombin to thrombin.

In 43 cases treated with dicumarol, this method was used. In a number of instances, parallel determinations were run with the one-stage method of Quick. It was found that the prothrombin values fell more rapidly in the beginning of treatment and returned more rapidly when dicumarol was discontinued, if the one-stage method was used. During treatment, the levels remained more constant with the stabilized thrombin method. Of the 43 cases followed, there were only 3 hyper-reactors (7 per cent) and only one (2 per cent) had a hemorrhage. This is compared to 16.6 to 27 per cent hyper-reactors and 4.7 to 40 per cent hemorrhagic complications in series where the one-stage method was used for the control of dicumarol therapy.

BEIZER

Lewis, J. H., Howe, A. C., and Ferguson, J. H.: Thrombin Formation. II. The Effects of Lysin (Fibrinolysin, Plasmin) on Prothrombin, Ac-Globulin and Tissue Thromboplastin. J. Clin. Investigation, **28:** 1507 (Nov.), 1949.

The authors studied the effects of serum lysin (fibrinolysin, plasmin) on several partially purified

components of a thrombin-forming system. They found that Ac-globulin was readily destroyed by lysin but prothrombin and thromboplastin were not affected. Some data suggested that thrombin may be slowly destroyed by lysin.

BUTTERWORTH

Alexander, B., and Landwehr, G.: Evolution of a Prothrombin Conversion Accelerator in Stored Human Plasma and Prothrombin Fractions. Am. J. Physiol. **159:** 322 (Nov.), 1949.

The authors discuss their experience with an agent which accelerates the conversion of prothrombin to thrombin by thromboplastin plus calcium. The agent as well as its precursor(s) can be adsorbed by barium sulfate and eluted with sodium citrate. It arises in hemophilic plasma, thrombocytopenic plasma, and in normal plasma handled entirely in siliconized apparatus. The accelerator cannot be demonstrated in the absence of a labile factor present in fresh plasma. The plasma prothrombin hyperactivity occurs at refrigerator temperature but not at body or room temperatures.

MOKOTOFF

Buckwalter, J. A., Blythe, W. B., and Brinkhous, K. M.: Effect of Blood Platelets on Prothrombin Utilization of Dog and Human Plasmas. Am. J. Physiol., **159:** 316 (Nov.), 1949.

By timing the rate of prothrombin utilization, it has been shown that the plasma of both dog and man contains platelets in excess of the minimal requirements for clotting. In terms of platelet count the requirements of dog plasma are about 1.7 times greater than those of human plasma.

MOKOTOFF

McIntire, F. C., Roth, L. W., and Richards, R. K.: The In Vitro Release of Histamine From Blood Cells of Sensitized Rabbits: Relationship to Blood Coagulation Mechanisms. Am. J. Physiol. **159:** 332 (Nov.), 1949.

It is suggested that thrombin, prothrombin, thromboplastin and Ac-globulin are not involved in the in vitro release of histamine by antigen from blood cells of sensitized rabbits. The histamine release mechanism is much more rapidly inactivated by citrate than is any part of the blood coagulation system.

MOKOTOFF

Quick, A. J.: The Coagulation Mechanism, with Specific Reference to the Interpretation of Prothrombin Time and a Consideration of the Prothrombin Consumption Time. Am. J. Clin. Path. **19:** 1016 (Nov.), 1949.

The author reviews the theory of blood coagulation and points out that platelets, on disintegrating, liberate an enzyme which activates the inactive precursor thromboplastinogen to thromboplastin. The latter immediately interacts with the prothrombin complex to form thrombin, an enzyme which converts fibrinogen to fibrin and also acts upon the platelets to increase their speed of disintegration.

The prothrombin time test measures prothrombin activity but furnishes no information concerning the thromboplastin concentration in the plasma. For the latter purpose the prothrombin consumption test has been developed; this consists of allowing blood to coagulate in a test tube and, after fixed periods of time, determining how much prothrombin remains in the serum. If the prothrombin consumption is normal, it indicates that both the platelets and the concentration of thromboplastinogen are normal. Using both the prothrombin time test and the prothrombin consumption test, the common hemorrhagic diseases can be classified as hypoprothrombinemias or thromboplastin deficiencies.

ABRAMSON

Milstone, J. H.: The Chain Reaction of the Blood Clotting Mechanism in Relation to the Theory of Hemostasis and Thrombosis. Blood **4:** 1290 (Dec.), 1949.

In a chain reaction, one of the products accelerates the reaction, with the result that as more product is formed the reaction goes increasingly faster. When the reaction velocity increases, the chain is said to be nonstationary. Autocatalytic reactions are a special group of nonstationary chain reactions and the term "chain reaction" includes other possible mechanisms.

In small punctures, one may suppose that the clot results from a mixture of blood and tissue juice, but in a larger cut, the deposition of such a coagulated film on the cut surface would prevent further coagulation. In a chain reaction such a film would incite the neighboring layer to clot and the coagulation process could be propagated from one layer to the next, with tissue juice needed only to influence the initial layer.

The author correlates available evidence to show that at least one chain reaction occurs during the coagulation of blood and appears to involve both the metamorphosis of platelets and the development of thrombokinase. This may make possible the growth of the hemostatic plug. It is likely that the chain reaction occurs in most instances where a thrombus forms and plays some part in its propagation. The presence of a countermechanism is also suggested since materials have been derived from blood which can reduce thrombokinase activity, inactivate thrombin and liquefy fibrin. These may help to maintain the fluidity of the circulating blood.

BEIZER

CONGENITAL ANOMALIES

De Rivera, A. G. R.: Congenital Heart Disease. Arch. d. enfer. d. corazon y vasos **46:** 13 (July), 1949.

The author reports the findings of his study of the anomalous origin of coronary arteries, vascular rings and aortic coarctation. He discusses the variations of the anomalous origin of the coronary arteries from the pulmonary artery, and stresses that subjective and objective manifestations may be apparent only when the left coronary artery arises in such a manner. Congenital vascular rings with tracheal and esophageal compression may be produced by retroesophageal branches from a left aortic arch, by a ligamentum arteriosus or ductus arteriosus and left subclavian artery arising from a right aortic arch, and by a double aortic arch. He discusses adult forms of coarctation of the aorta in which the ductus or ligamentum arteriosus inserts at or above the constricted site, and the infantile type in which the ductus remains open in communication with the descending aorta. He points out that frequently associated with coarctation there may be bicuspid aortic valves, hypertension, obliteration of the left subclavian artery and weakness or absence of pulsations in the lower extremities with retardation of the pulse wave.

SCHWEDEL

Grob, M.: The Anomalies of the Aortic Arch and their Embryological Development. Helvet. paediat. acta **4:** (Aug.), 1949.

The various anomalies of the aortic arch and its ramifications are described and their development explained with the help of many schematic drawings. The syndrome of "dysphagia lusoria" is of particular clinical importance. This is usually due to an anomalous origin of the left subclavian artery on the right side of the aorta. This vessel, by crossing the vertebral column from right to left, compresses the esophagus from behind and can be demonstrated by x-ray films taken in lateral position after filling the esophagus with barium. If a double aortic arch is present the ascending aorta divides into two limbs which meet again dorsally to form the descending aorta. Thus a vascular ring is formed by which the esophagus and trachea, or only the latter, may be compressed, leading to dysphagia and dyspnea. These clinical signs may improve spontaneously as subjects become older. In coarctation of the aorta the stenosis can be found proximal or distal to the subclavian artery; in the latter case it may be combined with a patent ductus arteriosus.

PICK

Prader, A., Rossi, E., and Wodenegg, M.: Investigations of the Blood in Morbus Caeruleus. I. The Plasma Volume and Blood Volume. Helvet. paediat. acta **4:** 267 (Aug.), 1949.

By means of a dye method (Geigy Blue), plasma and blood volume were determined in 20 cases of morbus caeruleus and compared with values found in 23 normal children. A definite increase of the blood volume (+65 per cent) was found in the former group due to a tremendous increase of the erythrocyte volume (+189 per cent). The plasma volume, however, was found to be slightly decreased (−17 per cent). The latter is considered by the authors as a compensatory mechanism which keeps the increase of the total blood volume within certain limits. Identical changes of plasma and blood volume can be found in cases of polycythemia resulting from high altitudes or in cases of polycythemia vera.

PICK

Holtmann, M.: The Electrocardiogram in Congenital Angio-Cardiopathies. Helvet. paediat. acta **4:** 244 (Aug.), 1949.

On the basis of standard limb leads and multiple V chest leads, the electrocardiographic findings in the different anomalies of the heart can be divided into five groups according to their clinical significance. (1) Definite evidence of a specific anomaly is offered only in the presence of a situs inversus. (2) The electrocardiogram can be diagnostic under certain conditions, e.g., if a coronary pattern is found in an infant (origin of a coronary artery from the pulmonary artery) or if complete A-V block is found in a child without evidence of a preceding inflammatory disease. (3) Not diagnostic per se, but characteristic, is a dextrocardiogram in the tetralogy of Fallot and a levocardiogram in tricuspid atresia or in persistence of a truncus arteriosus. (4) A dextrocardiogram is often, but not invariably, present in cases of abnormal drainage of the pulmonary veins into the right auricle, in isolated pulmonary stenosis, in Eisenmenger's complex and in transposition of the great vessels. If the latter is paired with an auricular septal defect, arrhythmias and A-V block may also be observed. A levocardiogram can be found in aortic stenosis, in coarctation of the aorta and in cases with a defect of the intraventricular septum. (5) The electrocardiogram is not characteristic in patent ductus arteriosus.

PICK

Soulie, P., Routier, D., and Bernal, P.: Defect of the Intraventricular Septum with Aortic Regurgitation (Differential Diagnosis from Patent Ductus Arteriosus). Arch. d. mal. du coeur **42:** 765 (Aug.), 1949.

Two patients, 5 and 11 years old, had the following findings in common: a known congenital anomaly of the heart, a continuous systolic and diastolic murmur in the left subclavicular region accompanied by a thrill; a hilar dance, a prominent pulmonary arch and enlargement of the left

ventricle on fluoroscopy; signs of combined ventricular strain in the electrocardiogram; a higher oxygen content in the blood obtained by catheterization from the pulmonary artery than in that obtained from the right ventricle. In addition, angiocardiography performed on the first case revealed simultaneous filling of the right ventricle, pulmonary artery and aorta. Both cases were considered to have a patent ductus arteriosus and were operated upon.

No patent ductus was found in the younger patient and the older patient died during operation. At autopsy of the latter a moderate dextroposition and insufficiency of the aortic valves, a prominent bulging of the intraventricular septum to the right, and a defect in its upper part were found. The ductus arteriosus was obliterated. The authors assume similar findings to have been present in their first case also. They emphasize the difficulties of the differential diagnosis of patency of the ductus and recommend caution in recommending operation if a continuous murmur is not found in such patients.

PICK

Grob, M., and Rossi, E.: The Diagnosis of Congenital Angio-Cardiopathies. Helvet. paediat. acta **4:** 189 (Aug.), 1949.

A discussion of the diagnosis of congenital malformations of the heart, including modern methods like catheterization of the right heart and angiocardiography is presented. One group of anomalies includes cases without intracardiac shunts. In isolated pulmonary stenosis, cyanosis is found to be either absent or only of slight degree, and in the angiocardiogram the filling of the pulmonary tree is decreased. In coarctation of the aorta cyanosis is likewise not found and the most important findings here are changes of pulses and blood pressures. Visualization of dilated collateral vessels is possible by angiocardiography. A second group of anomalies are those with a left to right shunt. If a defect of the auricular or ventricular septum is present, simultaneous filling of all four ventricular cavities is found in the later phases of the angiocardiograms. Of great importance here is the determination of the oxygen saturation in different chambers with the help of catheterization. The correct timing of a systolic-diastolic murmur within the heart cycle by phonocardiography is of help in the diagnosis of an open ductus arteriosus. In a third group are cases with signs of a right to left shunt. In the tetralogy of Fallot, dilated and tortuous capillaries can be seen in increased number by capillaroscopy and by examination of the eye ground. Further signs are hyperplasia of the gingiva and anomalies of the teeth. Especially characteristic is the absence of the shadow of the pulmonary artery at x-ray examination in contrast to Eisenmenger's complex which otherwise shows a clinical pattern similar to that of the tetralogy. In persistence of the truncus arteriosus, angiocardiography reveals early filling of the "aorta" together with inadequate filling of the pulmonary tree. Taussig's syndrome can be diagnosed by an angiocardiogram in the left anterior oblique position, which shows the origin of the pulmonary artery within the aortic shadow instead in front of it.

PICK

Maier, C., and Volkmann, M.: The Significance of the Gas Analysis in the Diagnosis of Congenital Heart Diseases. Helvet. paediat. acta **4:** 260 (Aug.), 1949.

Six typical cases of congenital heart disease, in which blood gas analysis was essential for the establishment of the correct diagnosis, are discussed. In the determination of the cardiac output and in the calculation of the amount of blood flow through intracardiac shunts, certain reservations have to be made since the error in such calculations, if based on Fick's formula, may attain values up to 20 per cent.

PICK

Howald, E.: A Case of Congenital Anomaly of the Heart with Abnormal Drainage of the Pulmonary Veins. Helvet. paediat. acta **4:** 322, (Aug.), 1949.

The author reports on the autopsies of two infants, 2 and 6 months old, respectively, with drainage of all pulmonary veins, connected to a common vessel, into the superior vena cava in the first case and into the vena hepatica in the second case. Marked excentric dilatation of the right auricle and right ventricle in both cases was due to the increased load put upon the right heart. After occlusion of the ductus arteriosus survival is possible only with persistence of a patent foramen ovale.

PICK

De Chastonay, E., and Buser, M.: A Case with Origin of the Left Coronary Artery from the Pulmonary Artery. Helvet. paediat. acta **4:** 308 (Aug.), 1949.

In a 5½ year old boy severe congestive heart failure with enormous cardiac dilatation mainly to the left was observed. The electrocardiogram revealed the pattern of anterior wall infarction. At autopsy an abnormal origin of the left coronary artery from the pulmonary artery was found. Due to the insufficient nutrition of the left ventricle, most of its muscle was replaced by collagenous connective tissue, leading to an aneurysmal dilatation of this chamber.

PICK

Grob, M., and Stockmann, M.: Coarctation of the Aorta. Helvet. paediat. acta **4:** 294 (Aug.), 1949.

The authors report the results of operation on 3 cases of coarctation of the aorta by the method of

Craaford. In all 3 cases the immediate response to the operation was a drop of the blood pressure in the upper extremities and an increase in the legs. The first two cases were improved by the operation; the third died suddenly four weeks after operation. At autopsy it was found that a fatal hemorrhage had occurred from a ruptured false aneurysm located at the line of suture in the aorta.

PICK

Doerr, W.: The Pathologic Anatomy of Congenital Cardiac Anomalies. Fortschr. a. d. Geb. d. Röntgenstrahlen **71:** 754 (Sept.), 1949.

The author describes the changes occurring during the development of the primitive vascular tube into the fully developed heart of a newborn infant and indicates the types of arrests in development such as incomplete septa, failure of rotation, and partial and incomplete incorporation of portions of the bulbus cordis into developing ventricles. He also discusses transposition of arterial trunks, coarctation, patent ductus arteriosus, and other common congenital cardiac defects. He states that 2.7 per cent of almost 29,000 autopsied cases of all ages had significant congenital cardiac defects.

SCHWEDEL

Catel, W.: Clinical Study of Congenital Heart Disease. Fortschr. a. d. Geb. d. Röntgenstrahlen. **71:** 769 (Sept.), 1949.

In a discussion of the major congenital anomalies the author cites the relative incidence of patent ductus Botalli as 36.9 per cent, interventricular septal defect as 33.6 per cent, varieties of pulmonic stenosis as 24 per cent, transposition of the major arteries as 3.3 per cent and aortic coarctation as 1.6 per cent. He differentiates among these lesions on the basis of cyanosis, heart size, murmurs, intensity of the second pulmonic sound, and the use of conventional roentgenographic examination.

SCHWEDEL

Perkins, G. B., Hammond, M. M., Dwan, P. F., and Shapiro, M. J.: Tetralogy of Fallot, Analysis of Forty-one Cases of Patients Treated Surgically at the University of Minnesota Hospitals. J. Pediat. **35:** 401 (Oct.), 1949.

The diagnostic findings and results of treatment by the Blalock-Taussig procedure in 41 tetralogy patients are reviewed. On the basis of both clinical and laboratory criteria, the authors conclude that good results were obtained in 26 patients, or 74.3 per cent of those having anastomoses performed. Five of those having anastomoses completed died, giving a mortality of 12.1 per cent. The total mortality was 19.3 per cent, including deaths in patients who had exploratory thoracotomies without anastomoses, and deaths which occurred after the patient had been discharged from the hospital. Among the more common postoperative complications noted were simple pleural effusion, chylothorax, Horner's syndrome, hoarseness and hemiplegia.

The need for operation and the risks involved can be best evaluated by information regarding the degree of arterial oxygen saturation, the patient's exercise tolerance, and arterial pressures measured directly by vascular and cardiac catheterization. Of particular value is the use of the Milliken-Smaller oximeter for determining the arterial oxygen saturation, although it is suggested that the comparative change in exercise tolerance after operation is more closely correlated with the clinical improvement of the patient than is the change in oxygen saturation levels.

SCHWARTZ

Alvord, R. M.: Coronary Heart Disease and Xanthoma Tuberosum Associated with Hereditary Hyperlipemia. Arch. Int. Med. **84:** 1002 (Dec.), 1949.

The author presents a survey of a family in which 15 members had hyperlipemia, 6 had xanthoma tuberosum and 18 had a history suggesting disease of the coronary arteries. A disturbance in lipid metabolism appeared to be the basic inherited defect and hyperlipemia (hypercholesteremia) appeared to be inherited as a simple autosomal dominant trait. Xanthoma tuberosum, xanthelasma, arcus senilis, angina pectoris and possibly xanthomatous involvement of the myocardium and valves were complications arising from prolonged hyperlipemia in this family. In general, these complications arise in the fifth and sixth decades of life with the exception of xanthoma tuberosum which usually occurs at an earlier age. Treatment of this condition is entirely symptomatic, and the theoretic use of lipotropic substances to keep the serum cholesterol and other serum lipids at a normal level and thus eliminate the complications of prolonged hyperlipemia has, as yet, given inconclusive results.

BERNSTEIN

Maier, H. C., and Bortone, F.: Complete Failure of Sternal Fusion with Herniation of Pericardium. Report of a Case Corrected Surgically in Infancy. J. Thoracic Surg. **18:** 851 (Dec.), 1949.

Complete failure of sternal fusion with a defect extending the entire length of the anterior thorax is a very rare occurrence. Such a congenital maldevelopment of the sternum may be associated with ectopia cordis. Due to the lack of a rigid thoracic cage at the site of the sternal defect, considerable paradoxical motion may occur with resultant respiratory and cardiocirculatory difficulty. If only a partial cleft sternum or a narrow sternal fissure is present, symptoms may be slight or absent.

The embryological development of the sternum is briefly reviewed. A case of complete lack of fusion of the entire length of the sternum with

herniation of the pericardium is reported. This is apparently the first case reported in which such a congenital defect was successfully corrected by surgery in infancy. The importance of performing the operation very shortly after birth is well illustrated by this case. The relationship between cleft sternum and ectopia cordis is discussed briefly.

BECK

Stephens, H. B., and Grimes, O. F.: Coarctation of the Aorta. Report of Six Cases with Operation. J. Thoracic Surg. **18:** 804 (Dec.), 1949.

Six patients exhibiting coarctation of the aorta were operated upon; three patients survived. One fatality was operative; two others, from exsanguinating hemorrhage, occurred in the immediate postoperative period. One of these resulted from necrosis at the line of anastomosis; the other, although showing but little evidence of healing at the suture line, had a small perforation proximal to the line of anastomosis. The operative death, in retrospect, was probably a preventable one.

A brief review of the literature indicates that an over-all mortality rate of 22.5 per cent exists for the surgery of coarctation of the aorta. Most of the reported deaths have occurred in patients in older age groups and the most common cause of death has been hemorrhage, usually at the line of anastomosis. It is quite generally agreed that an end-to-end aortic anastomosis is the procedure of choice. There are probably no absolute contraindications to the surgery of the adult type of coarctation of the aorta. In most instances, surgery remains the only hope even for those in whom the operative risks are great but within the realm of reason; these patients should be offered the benefit of operative therapy.

BECK

Burford, T. H., Carson, M. J., and Scott, W. G.: Angiocardiography and Aortography in the Diagnosis of Congenital Cardiovascular Lesions. J. Thoracic Surg. **18:** 860 (Dec.), 1949.

The necessary conditions and technique for successful angiocardiography are described. Eighty-six visualizations were performed, 63 of which were intravenous angiocardiograms and 23 of which were retrograde aortograms. From operations and postmortem angiocardiograms on this group, there was but one wrong diagnosis. There were no deaths or untoward events ascribable to the dye or the method. In the retrograde group there were no complications attributable to the use of the carotid artery. Although angiocardiography and retrograde aortography should not supplant physiologic studies or simple examination and fluoroscopy, they do give direct information as to the course of intracardiac blood flow and relative size and location of the cardiac chambers and great vessels when properly done, and are of the greatest value in establishing the exact diagnosis in borderline cases of congenital heart disease which is applicable to all age groups.

BECK

Swyer, A. J., Mauss, I. H., and Rosenblatt, P.: Congenital Diverticulosis of the Left Ventricle. Am. J. Dis. Child., **79:** 111 (Jan.), 1950.

The authors report a case of a 38 hour old infant apparently normal at birth who suddenly became cyanotic and died almost immediately thereafter. At autopsy there was found in the ventricular pocket behind the aortic cusp of the mitral valve, an opening which was lined with endocardium continuous with that of the left ventricle. This opening led into a diverticulum which bifurcated, forming two bulbous sacs 0.09 centimeters in diameter. These projected posteriorly and laterally, lying against the medial wall of the left atrium and the left side of the pulmonary artery; they contained all of the heart layers. There was a perforation of one sac and the apex of the other sac was paper thin. Both sacs contained thrombotic material. The pericardial cavity contained 60 cc. of blood. The ductus arteriosus was patent and there was partial collapse of the lungs.

The anatomic diagnoses were diverticulum of the heart with rupture, hemopericardium, patent ductus arteriosus, atelectasis, and congestion of the viscera.

MARGOLIES

Taylor, B. E., Knutson, J. R. B., Burchell, H. B., Daugherty, G. W., and Wood, E. H.: Patent Ductus Arteriosus Associated with Coarctation of the Aorta: Report of 2 Cases Studied before and after Surgical Treatment. Proc. Staff Meet., Mayo Clin., **25:** 62 (Feb.), 1950.

In the series collected by Maude Abbott, approximately 10 per cent of all patients with the adult type of coarctation had an associated patent ductus arteriosus. The authors present in detail two such cases. In each instance the exact diagnoses were made possible by catheterization of the heart. However, the differentiation of this associated defect from a bicuspid aortic valve with insufficiency may be difficult clinically. Likewise, in making a diagnosis of a patent ductus arteriosus it is always necessary to consider that a coarctation of the aorta may also be present. In patients with a patent ductus arteriosus opening to the aorta distal to a stricture of the aorta, as in the second case, it is not uncommon for the flow of blood to be from the pulmonary artery to the aorta, thus producing a subnormal oxygen saturation of the blood flowing to the lower part of the body.

SIMON

Taylor, B. E., and DuShane, J. W.: Patent Ductus Arteriosus Associated with Pulmonary Stenosis. Proc. Staff Meet., Mayo Clin. **25:** 60 (Feb.), 1950.

Electrocardiographic evidence of right ventricular hypertrophy in a patient with the diagnosis of patent ductus arteriosus should make one suspect the presence of some other lesion, particularly a pulmonic stenosis. Such was the situation in the reported case of a 5 year old boy who was subjected to cardiac catheterization. That the right ventricular pressure in this boy was only moderately elevated would be in agreement with the opinion that the pulmonary stenosis was not severe. Theoretically then, not only should he tolerate ligation of the ductus arteriosus, thus removing a possible site for infection and decreasing the load on the left side of the heart, but it is possible that the pulmonary blood flow would be facilitated.

In view of the recent developments in cardiac surgery, especially valvulotomies, the parents were advised to postpone closure of the ductus. It was hoped that a few years later operation might be performed and at that time, in addition to closure of the patent ductus arteriosus, the pulmonary obstruction might also be alleviated.

SIMON

Knutson, J. R. B., Taylor, B. E., Pruitt, R. D., and Dry, T. J.: Anomalous Pulmonary Venous Drainage Diagnosed by Catheterization of the Right Side of the Heart. Report of 3 cases. Proc. Staff Meet., Mayo Clin., **25:** 52 (Feb.), 1950.

During catheterization of the right side of the heart, the authors found 3 cases in which there was anomalous pulmonary venous drainage. In 2 of these cases the catheter was passed into an anomalous pulmonary vein, and in the third the oxygen saturations in the superior vena cava revealed this abnormality. The anomalous drainage of pulmonary veins into the right side of the heart increases the oxygen saturation of the blood in the recipient chamber or vessel, as well as that of the right ventricle and the pulmonary arteries. In addition to increasing the oxygen saturation, it increases the pulmonary flow. This recirculation of blood results in engorgement of the pulmonary bed, adds to the work of the right side of the heart, and leads to right ventricular hypertrophy.

The heart was enlarged in all 3 cases as shown by roentgenogram. The auricles were fibrillating in 2 of these cases. Electrocardiographic evidence of right ventricular hypertrophy was evident in 2 of the cases and the third case showed right bundle-branch block, a finding which is consistent with right ventricular hypertrophy. In one case there was no murmur, in one there was a systolic murmur and in one there were both systolic and diastolic murmurs. The life expectancy, as judged by study of a group of cases collected from the literature, is better for cases of partial pulmonary drainage into the right atrium than for atrial septal defects.

Surgical therapy of a type designed to obliterate pulmonary blood flow to the anomalously drained portion of the lung was deferred because of the statistically favorable prognosis and because of further potential developments in reconstructive surgery wherein transplantation of veins might be done. An important consideration in this regard is the fact that the lung with abnormal pulmonary drainage may serve as an emergency respiratory organ if acute pulmonary disease in the normally drained lung and subsequent inadequate oxygenation of the blood in this lung should develop.

SIMON

Burchell, H. B., and Wood, E. H.: Remarks on the Technic and Diagnostic Applications of Cardiac Catheterization. Proc. Staff Meet., Mayo Clin., **25:** 41 (Feb.), 1950.

In the diagnosis of congenital malformations of the heart, cardiac catheterization has an established place, but the data obtained may not always be easy to interpret. The catheterization procedure cannot be simplified to any extent if the maximum diagnostic data are to be obtained. When the procedure is used for other specific purposes and the heart is free of intracardiac defect, simplification of the procedure is possible. Artefacts in the pressure recordings through the catheter remain a problem but do not appear to interfere significantly with anatomic diagnoses. The data of the authors indicate that when the pulmonary artery is dilated, there is often a systolic pressure gradient petween the right ventricle and pulmonary artery.

One case of moderate pulmonary stenosis without electrocardiographic or roentgenologic evidence of right ventricular hypertrophy is reported. The ear oximeter and the cuvette oximeter are of great value in the catheterization procedure.

SIMON

CONGESTIVE HEART FAILURE

Lorenzoni, B., and Lenzi, E.: Particular Behavior of Venous Pressure in Some Patients with Congestive Failure. Folia cardiol. **8:** 243 (June), 1949.

The authors observed, in several patients with congestive failure, a paradoxical phenomenon which consisted of a marked increase of the venous pressure during deep inspiration. The authors discuss several possible causes. High excitability of the venomotor center does not seem probable. Increased excitability of the venous wall, on the other hand, is not considered sufficient to rapidly increase the venous pressure. Compression of the congested liver by the diaphragm followed by an increased venous return seems the most likely cause. However, more than one factor may be operative.

LUISADA

Wahi, P. N., and Mathur, K. S.: Splenomegaly in Congestive Heart Failure. Indian Heart J. **1:** 230 (Sept.), 1949.

In 81 of 690 cases of congestive failure the spleen

was studied clinically as well as histologically. The material for histological examination was obtained from 31 autopsies and 50 puncture biopsies. The spleen on the average was increased above the normal weight. In 22.2 per cent cases of uncomplicated congestive failure, the spleen was large enough to be theoretically palpable, i.e. 300 grams. Clinically the spleen was found palpable only in 7.4 per cent of the cases. The duration of congestive heart failure did not appreciably influence the size of the spleen or its weight at autopsy.

In 6.4 per cent of the cases, the liver was large enough to be theoretically palpable. However, in the clinical study of 690 cases, the liver was reported palpable in 61 per cent of cases. The spleen on the average showed greater enlargement by weight than did the average liver in cardiac decompensation. Histological studies suggested that splenic enlargement is due to congestion of the spleen which later may be aggravated by the onset of portal hypertension.

BERNSTEIN

Buylla, P. A., and Garcia Barbon, V. B.: Treatment of Congestive Heart Failure by Antithyroid Substances. Rev. españ. de cardiol. **3:** 453 (Sept.–Oct.), 1949.

The authors discuss the treatment of congestive heart failure by thiouracil derivates. Their discussion deals with the pathophysiological aspects of this treatment and includes such problems as artificially induced hypercholesterolemia and tendency to retention of fluid, which, if caused by this antithyroid treatment, might theoretically be harmful to the patient; however, they do not regard these considerations as valid contraindications to the treatment. The authors favor the administration of small doses of the antithyroid drugs in order to avoid the establishment of a myxedematous state. After the clinical state is improved, they continue with still smaller maintenance doses, e.g., .05–.10 Gm. daily, of methyl thiouracil. Their own experience is based on more than 200 cases; 8 cases are described in detail. The results were excellent, and remained so for periods up to nine months after the intensive treatment was discontinued. No severe toxic phenomena occurred; they encountered occasional slight transitory leukopenia and skin reactions.

ULLMANN

Davis, J. O., and Shock, N. W.: The Effect of Theophylline Ethylene Diamine on Renal Function in Control Subjects and in Patients with Congestive Heart Failure. J. Clin. Investigation **28:** 1459 (Nov.), 1949.

The effect of theophylline ethylene diamine on renal function was studied in 25 control subjects and in 6 patients with congestive heart failure. The mechanism of action, according to the authors, is evidently twofold, with an increase in excretion of sodium and water being associated with (1) an elevation in glomerular filtration rate and (2) a decrease in renal tubular reabsorption. It seemed likely, but was unproved, that a decrease in tubular reabsorption contributed to a sustained diuresis more than did an augmented filtration rate. There was no evidence that salt and water retention in decompensated patients was the result of a low glomerular filtration rate, and it is felt that the cause of renal impairment in cardiac failure is to be sought in a study of the tubular reabsorptive mechanism of sodium.

BUTTERWORTH

CORONARY ARTERY DISEASE, MYOCARDIAL INFARCTION

Grelland, R.: Perforation of the Infarcted Interventricular Septum Diagnosed Ante Mortem. Acta med. Scandinav. **133:** 1 (March–June), 1949.

Rupture of the interventricular septum as a result of coronary occlusion with infarction is a relatively rare occurrence, and the condition has only occasionally been diagnosed clinically. The author reports a case of perforation of the interventricular septum resulting from coronary occlusion in which the condition was diagnosed ante mortem. The patient presented typical symptoms of infarction of the heart, and his condition was fairly good until the ninth day when acute symptoms of right heart failure associated with physical signs of a septal defect developed. The patient died twenty-four days after the occurrence of the infarction and fifteen days after the septal perforation. At autopsy a thrombus was found in the right coronary artery with infarction of the posterior part of the septum. In the anterior, lower part of the infarcted area a perforation with a diameter of 1 cm. was found. Patients with rupture of the septum differ from patients with other types of cardiac rupture in that they live longer after the rupture and do not die so suddenly and unexpectedly.

BELLET

Bredt, H.: The Special Position of Juvenile Coronary Sclerosis and the Histological Basis of Acute Coronary Insufficiency. Beitr. z. path. Anat. u. z. allg. Path. **110:** 295 (May), 1949.

In comparing coronary pathology in younger and older age groups, the author used only patients with very marked changes and a lethal event in the younger group. His observations during the last eight years indicate a noticeable increase of the incidence of the disease in the age group of 20 to 30 years. In contrast to coronary sclerosis of the aged and in accordance with figures known for endangiitis obliterans, the incidence among males is about ten times that in females. Histologically, juvenile sclerosis resembles the pattern seen in Winiwarter's disease by its focal appearance in a single vessel, and by more marked proliferation of the intima with

early obliteration of the lumen, fibrinoid degeneration and cellular infiltration of the subendothelial layers. These changes in the wall of the vessel are the basis for the terminal event of edema in the thickened intimal layers and sudden formation of a thrombus, probably due to an inflammatory reaction. In this connection the author mentions the paradentosis found in all seven of his cases.

PICK

Gauwerky, F.: The Roentgen Appearance of Calcification of the Coronary Arteries. Fortschr. a. d. Geb. d. Rontgenstrahlen **71:** 743 (Sept.), 1949.

The author describes two instances of calcification of coronary arteries. These were seen as calcified double tracks 4 to 5 mms. apart, extending along the course of the major coronary arteries. In the first case the right coronary artery was demonstrated in the left anterior oblique as a convex density anteriorly and to the right. In the posteroanterior view this was noted just to the right of the spine within the cardiac shadow. Calcifications noted in the region just below the pulmonary arterial trunk were thought to be present at the junction of the left anterior descending and left circumflex arteries.

In the second case a calcified double-track density was noted extending to the left in the posteroanterior view and anteriorly and centrally in the left anterior oblique view. This was thought to represent the left anterior descending coronary artery. The basis for such localization was confirmed by injecting opaque gelatin material into a heart removed at necropsy and projecting it in the posteroanterior and left anterior oblique views.

SCHWEDEL

McManus, J. F., and Lawler, J. J.: Myocardial Infarction following the Administration of Tetanus Antitoxin. New England J. Med. **242:** 17 (Jan.), 1950.

The occurrence of myocardial infarction as a complication of serum sickness is rare. The authors found only three reports in the literature in which tetanus antitoxin resulted in serum sickness and myocardial infarction. The authors report the case of a 32 year old man in whom no evidence of arteriosclerotic, hypertensive or syphilitic heart disease was present. Serum sickness followed the administration of 1500 units of tetanus antitoxin. Accompanying this serum sensitization the patient presented symptomatic as well as electrocardiographic evidence of a posterior myocardial infarction. The infarction eventually healed and the patient recovered. The authors postulate that the serum sickness resulted in coronary arteritis comparable to that produced in animals by the injection of horse serum.

NADLER

ELECTROCARDIOGRAPHY

Altana, G.: Singular Electrocardiographic Picture Caused by Quinidine. Folia cardiol. **8:** 189 (June), 1949.

A rare electrocardiographic picture was observed during treatment with quinidine sulfate of a digitalized patient with auricular fibrillation. The dose of the drug did not exceed 1 Gm. a day. After reestablishment of the sinus rhythm, the Q-T interval became unusually long, (0.64 sec.) with a rate of 50. The phenomenon is attributed to toxic effect of quinidine.

LUISADA

Soulié, P., Laham, J., Papanicolis, I., and Voci, G.: The Principal Electrocardiographic Types of Combined Heart Strain. Arch. d. mal. du coeur **42:** 791 (Aug.), 1949.

Fifty-seven cases of bilateral ventricular hypertrophy, either proved at autopsy or suggested by clinical and x-ray findings, were studied electrocardiographically by the use of unipolar limb and chest leads. Four types of electrocardiograms could be distinguished.

In the first group, considered pathognomonic of combined heart strain, the authors found right axis shift, signs of marked clockwise rotation of the heart, and signs of right-sided as well as left-sided hypertrophy in the precordial leads. In a second group mitral and aortic lesions were found especially frequently; these patients presented the pattern of left heart strain in an electrically vertical heart with clockwise rotation along the longitudinal axis. In a third group, signs of left heart strain were present in the chest leads, while the electrical axis was normal or slightly shifted to the left, depending on the electrical position of the heart semivertical, intermediate or semihorizontal. This group comprised cases of arterial hypertension, aortic valvulitis or combined mitral and aortic lesions with predominance of the aortic lesion. A fourth group, in which arterial hypertension and aortic stenosis were frequent, was characterized by signs of left heart strain in the limb leads and a displacement to the left of the transitional zone in the precordial leads. The electrical position in this group was generally horizontal with counterclockwise rotation along the longitudinal axis with the apex pointing backwards.

The diagnostic value of these four types is variable. Whereas type I is pathognomonic, type II is only suggestive of combined heart strain. Types III and IV do not permit the diagnosis. However, in the author's opinion none of the four types is significant enough to warrant the diagnosis of combined heart strain if it is not in accordance with clinical and x-ray findings.

PICK

Frischknecht, W.: The Orthostatic Electrocardiogram in Children with Lability of the Vegetative

Nervous System. Helvet. paediat. acta, **4:** 327 (Aug.), 1949.

In 50 children with signs of lability of the vegetative nervous system, extreme and average values of changes occurring in the electrocardiogram in standing position were correlated with orthostatic variations of the blood pressure. The author paid particular attention to changes in the heart rate and to changes in the angle of the R and T vectors constructed for the frontal plane from the three standard leads. The average angle was found to be 29° in supine position; it changed to 61° after ten min. of standing.

The orthostatic changes in the electrocardiogram occur independently of other orthostatic symptoms, e.g., without change of the sinus rate. Variations of the vegetative tone during the day may also influence the orthostatic electrocardiogram. An abnormal orthostatic tracing indicates the presence of some disharmony in a complex vegetative regulation mechanism. A normal orthostatic electrocardiogram does not exclude the presence of a vegetative disharmony in other parts of the nervous system.

PICK

Stevenson, I. P., Duncan, C. H., Wolf, S., Ripley, H. S., and Wolff, H. G.: Life Situations, Emotions, and Extrasystoles. Psychosom. Med. **11:** 257 (Sept.–Oct.), 1949.

To study the relation of extrasystoles to life situations, 12 unselected patients were carefully evaluated. After a life history and a personality study were completed, electrocardiograms were taken during interviews at which pertinent topics were discussed.

Anxiety was a prominent feature in 11 of the 12 patients; 8 showed sinus tachycardia repeatedly. As a group they were timid, dependent and somewhat passive. Long-standing anxiety, more recently accentuated and focused on the heart, was common. Relief of anxiety was consistently associated with abolition of the extrasystoles.

While emotional disturbances may precipitate attacks of extrasystoles, the underlying susceptibility of the heart to neural excitation must be recognized. Prolonged hyperactivity of cardiac muscle during anxiety strains the heart, particularly if there is structural disease. (Two-thirds of the cases in this group had structural damage.) Such hearts are particularly prone to develop altered excitability.

The occurrence of an arrhythmia in patients with organic heart disease should draw attention to some environmental stress to which the subject is reacting with defensive mobilization beyond his heart's capacity. Therapy should include alteration of the life situation and the patient's adjustment to it, if possible, to relieve the stress on the heart, of which extrasystoles are an indication.

WAIFE

Sargent, F. K., and Gillespie, J. B.: Recurrent Paroxysmal Tachycardia in Infancy. Arch. Pediat. **66:** 437 (Oct.), 1949.

The authors present a case of tachycardia in an 11 day old infant which was unrecognized as a cardiac arrhythmia until the infant was 6 weeks of age, at which time an electrocardiogram revealed the rapid rate to be due to an auricular tachycardia. Digitalis in doses of ¼ cat unit every three hours for three or four doses reverted the tachycardia to a slow normal rhythm, but a maintenance dose of digitalis failed to prevent further paroxysms of the tachycardia. However, the combination of digitalis and quinidine was successful in preventing the auricular tachycardia. In two autopsied cases of paroxysmal tachycardia the authors observed a rhabdomyoma of the heart in one and two aberrant bundles of cardiac muscle tissue in the other.

LECKS

Ljung, O.: The Electrocardiogram in Hypocalcemia with Special Reference to the T-Wave. Acta med. Scandinav. **136:** 56 (Nov.), 1949.

A series of 28 cases of hypocalcemia was studied in reference to electrocardiographic changes. All the patients had serum calcium levels of 7.5 mg. per cent or less at some time during the period of study. In one, hypocalcemia was due to an enterogenous disturbance, in 7 to chronic nephritis, and in 20 there was postoperative hypocalcemia. The Q-T interval was prolonged in all cases. Of 18 cases of postoperative hypocalcemia without hypothyroidism, abnormally low T waves in Leads I and/or II were noted at times in 11. As serum calcium values returned to normal in response to vitamin D therapy, the Q-T interval and T waves usually returned to normal. An attempt at restoring the T wave to normal by injecting ergotamine was made in 4 cases, and in 2, abnormal T waves became normal in response to this treatment. Other than the changes in the Q-T interval and T waves, no changes were found in the electrocardiograms of these patients which might have been produced by hypocalcemia.

SCHWARTZ

Garcia Barbon, V. B.: Paroxysmal Ventricular Fibrillation, Rev. españ. de cardiol., **3:** 531 (Nov.–Dec.), 1949.

The author stresses the frequency of paroxysmal ventricular fibrillation as a cause of sudden cardiac death and of Stokes-Adams syndrome. As this latter condition is usually caused by ventricular arrest, the correct diagnosis of ventricular fibrillation may be of therapeutic importance. If paroxysmal ventricular fibrillation lasts for more than a few seconds, the attack usually causes death. The author's case, a 54 year old woman with severe hypertension, had a series of more than 130 attacks in three days. Clinically, some of the periods of unconsciousness and absence of pulse lasted for six minutes or more.

Electrocardiograms obtained during several attacks showed ventricular fibrillation with large irregular waves, with a rate of 400 to 600 per minute. After the attacks subsided, the patient developed clinical and electrocardiographic evidence of posterior wall infarction with complete A-V block. Since the attacks occurred before infarction became manifest, the author deems it possible that a relative ischemia in a "fibrillogene zone" brought on the attacks, and that their termination might have been due to the complete subsequent destruction of this zone. Other possibilities to explain the termination of the attacks are the fall in blood pressure which followed the infarction, or the therapy which consisted in magnesium sulphate and morphine, both given intravenously. The patient was followed for more than one month, during which time she was clinically well but still showed complete A-V dissociation with a ventricular rate of 30 per minute.

ULLMANN

Berman, B., and McGuire, J.: Electrocardiographic Changes Induced by Cold Application to Various Body Sites in Patients with Angina Pectoris—Preliminary Report. Am. J. M. Sc. **219:** 82 (Jan.), 1950.

The refrigerator ice cube, held in contact with the patient's skin, was used in 20 patients with coronary arteriosclerosis and angina of effort. Electrocardiographic changes with or without pain were induced in some of the cases. The necessity for particular protection of certain body areas of patients with angina of effort in the presence of cold is emphasized. It is suggested that minimal cold application, particularly following meals, may be of clinical value in detecting coronary insufficiency.

DURANT

HYPERTENSION

Flasher, J., and Drury, D. R.: Effects of Removal of the "Ischemic" Kidney in Rabbits with Unilateral Renal Hypertension, as Compared to Unilateral Nephrectomy in Normal Rabbits. Am. J. Physiol. **158:** 438 (Sept.), 1949.

Hypertension may be induced in the rabbit by latex encapsulation of one kidney, hypertensive readings being obtained usually between the fifteenth and sixtieth day following the procedure. Removing the ischemic kidney in 7 hypertensive rabbits failed to alter the pressure readings immediately in 4 animals, although normal pressures were finally recorded after 23, 48 and 152 days (one rabbit was removed from the series after eleven days). The results represent another example of the self-perpetuating effects of artificially induced hypertension.

HECHT

Modell, A. H., and Potter, H. W.: Human Figure Drawing of Patients with Arterial Hypertension, Peptic Ulcer, and Bronchial Asthma. Psychosom. Med. **11:** 282 (Sept.–Oct.), 1949.

A drawing of the human figure is recognized as a projection of the personality of the subject. In this study 32 patients including 10 with hypertension drew "a person." The drawings were interpreted with the object of delineating personality traits.

Disturbances in the psychosexual sphere and wariness and suspicion of the environment were common to asthmatic, peptic ulcer and hypertensive patients. As a group, the hypertensives depicted themselves as weakened, inadequate individuals. A need for personal assertiveness was prominent in the drawings. Marked social withdrawal was noted in those patients who showed exaggerated attempts to contact the environment. Some significant differences were found in the characteristics exhibited by the asthmatic and peptic ulcer groups.

WAIFE

Smithwick, R. H.: An Evaluation of the Surgical Treatment of Hypertension. Bull. New York Acad. Med., **25:** 698 (Nov.), 1949.

The author discusses the effect upon hypertension of unilateral nephrectomy and removal of adrenal tumors but, principally, he considers his experience with operations on the sympathetic nervous system. The two principal known actions of sympathectomy are modification of blood pressure levels and modifications of the reflex regulation resulting from the inactivation of important components of the vasoconstrictor mechanism. Presumed effects of sympathectomy are abolition of reflex secretion of adrenalin and stabilization of blood flow through the denervated vascular bed.

The author states that in his own experience 66 per cent of unselected hypertensives with cardiovascular changes have a slight to marked reduction in blood pressure lasting one to five years, but this falls to 47 per cent for the five to ten year follow-up group. The operative mortality is about 1 per cent but is higher if a transthoracic approach to include cardiac innervation is used. This latter technique is used in about 20 per cent of cases because of tachycardia and postural hypotension. Evaluation of all cases after five to ten years indicates that hypertension is favorably modified by sympathectomy as judged by eye grounds, electrocardiograms, blood pressure and total mortality although the author admits the difficulty of finding comparable case reports on unoperated hypertensives.

A plan for evaluating cases for sympathectomy is presented. The plan utilizes a graded numerical system with points allocated for abnormalities such as abnormal electrocardiogram, enlarged heart, renal and cerebral changes. The higher the point score, the poorer the risk. Cases can be divided into 5 groups depending upon this numerical point score and other factors such as sex and resting diastolic blood pressure. The author feels that his groups 1,

2, and 3 which represent earlier stages of the disease can be favorably modified by sympathectomy, while the prognosis in groups 4 and 5 has not been affected by sympathectomy so the operation is contraindicated in patients falling into these groups.

BUTTERWORTH

Comwell, P. M.: Hypertension due to Partial Renovascular Occlusion. New England J. Med., **241:** 1006 (Dec.), 1949.

The author describes the course of events in a known normotensive patient who developed hypertension at a time when incomplete arterial occlusion of the right renal artery was demonstrated at operation. Removal of the affected kidney was accompanied by a return of blood pressure to normal. Pathologic study of the excised kidney showed a normal cortex with necrosis of the medullary portion. The specific cause of the vascular occlusion was not determined; the author theorized that an atheromatous plague might have been present at the origin of the right renal artery. Normal blood pressure was maintained during observation for eighteen months after nephrectomy.

NADLER

Kohári-Kucharik, J.: The Effect of a War-Imposed Protein-Free Diet on the Blood Pressure Level in Essential Hypertension. Am. J. M. Sc. **219:** 27 (Jan.), 1950.

In Budapest in 1945 there was a complete protein famine following the siege of that city. This circumstance permitted the making of observations on the influence of an animal protein-free diet on hypertension. The observations were carried out on out-patients who had been under treatment for two to five years. The protein-free diet lasted from January up to the autumn of the same year, a period of ten months. Thirty-nine patients with long standing essential hypertension did not show any consistent change in blood pressure after this long period of protein deprivation.

DURANT

PATHOLOGIC PHYSIOLOGY

Soulié, P., Carlotti, J., Joly, F., and Sicot, J. R.: Catheterization of the Sinus Coronarius (A Study of 11 Cases). Arch. d. mal. du coeur **42:** 818 (Aug.), 1949.

In 7 cases of congenital heart disease, in two cases of mitral stenosis and in two cases of emphysema, a cardiac catheter was introduced into the coronary sinus, 6 times by chance and 5 times deliberately. If certain precautions are observed, this procedure is not difficult, is harmless, and permits the study of coronary flow and its variations. Unintentional catheterization of the sinus coronarius may become a source of error in the exploration of the right ventricular cavity if only radioscopic control of the position of the catheter is used. The correct localization of the tip of the catheter within the coronary sinus can be made (a) from the course of the catheter, which is less oblique if it enters the pulmonary artery and less high if it enters the right ventricular cavity; (b) visible pulsations of its tip which are in contrast to the low pressure values obtained in this position; (c) from the contour of the pressure curve; and (d) from the unusual low oxygen saturation of blood samples.

PICK

Neil, E., Redwood, C. R. M., and Schweitzer, A.: Pressor Responses to Electrical Stimulation of the Carotid Sinus Nerve in Cats. J. Physiol. **109:** 259 (Sept.), 1949.

Although considerable evidence has accumulated indicating that a rise of pressure in the carotid sinus causes reflexly a fall of systemic blood pressure, only few observations are present in the literature regarding the effect of electrical stimulation of the nerve trunk innervating this structure. The authors studied this problem in cats anesthetized with chloralose; a rectangular wave electronic stimulator and also the conventional induction coil were used. In the great majority of cases, stimulation of the carotid sinus nerve produced a rise in blood pressure. This type of response was unaffected by double vagotomy, destruction of the contralateral carotid sinus nerve, section of the homolateral glossopharyngeal nerve peripheral to its junction with the carotid sinus nerve, homolateral cervical sympathectomy, sectioning of the homolateral carotid sinus nerve near its origin from the carotid sinus, and bilateral adrenalectomy. However, the pressor effect was abolished by high cervical spinal transection or section of the glossopharyngeal nerve central to its junction with the carotid sinus nerve. When Nembutal anesthesia was substituted for the chloralose, a depressor response to stimulation of the carotid sinus nerve was elicited. From such evidence it was concluded that chloralose diminishes the sensitivity of the baroceptors in the carotid sinus to hydrostatic pressure changes and inhibits the vasomotor center response to baroceptor stimulation. Under such conditions, stimulation of the carotid sinus nerve trunk essentially excites only the afferent fibers arising from the chemoreceptors of the carotid body, causing a rise of blood pressure.

ABRAMSON

Borden, C. W., Ebert, R. V., Wilson, R. H., and Wells, H. S.: Studies of the Pulmonary Circulation. II. The Circulation Time from the Pulmonary Artery to the Femoral Artery and the Quantity of Blood in the Lungs in Patients with Mitral Stenosis and in Patients with Left Ventricular Failure. J. Clin. Investigation **28:** 1138 (Sept.), 1949.

Using the methods described in Part I, the au-

thors studied 10 patients with rheumatic heart disease and mitral stenosis. These subjects had exertional dyspnea and some degree of pulmonary hypertension. In addition, 18 men with aortic valve or hypertensive heart disease and left ventricular failure were similarly investigated. The mean pulmonary artery-femoral artery circulation time was prolonged and the cardiac output reduced in both groups. In the mitral stenosis group there was no evidence of a large increase in circulating blood in the lungs, left heart, aorta and certain large arteries. On the other hand, there was a marked increase in the blood volume of this part of the circulatory system in the patients with left ventricular failure. This may have been due to an increase in the amount of blood in the left ventricle in these patients. No correlation was found between reduction in vital capacity and the volume of blood in the aforementioned system (chiefly pulmonary blood volume). This would suggest that a reduced vital capacity in cardiac patients is not a direct function of increased pulmonary blood volume.

WAIFE

McCann, W. S., Bruce, R. A., Lovejoy, F. W., Jr., Yu, P. N. G., Pearson, R., Emerson, E. B., Engel, G., and Kelly, J. J.: Tussive Syncope. Arch. Int. Med. **84:** 845 (Dec.), 1949.

The background of Charcot's syndrome of laryngeal epilepsy is reviewed, and the laboratory findings in two similar cases are described. Both the Valsalva maneuver and paroxysmal coughing were found to impede venous return and pulmonary circulation and to decrease the cardiac output. Cerebral congestion alone was not sufficient to cause syncope, but cerebral congestion occurred in addition to anoxemia and cerebral anoxia with decreased cardiac output. In the first patient, syncope and even convulsions were produced by the Valsalva maneuver while he was in the recumbent position. The possibility that spasm of the pulmonary artery occurred, in addition to a pronounced increase in intrathoracic air pressure, was investigated with inconclusive results. The term "tussive syncope" is believed to be more appropriate than "laryngeal epilepsy" since the syncopal response is dependent on circulatory disturbances due to coughing and is not due to epilepsy.

BERNSTEIN

Harrison, W., and Liebow, A. A.: Gas Exchange in the Lung Deprived of Pulmonary Arterial Supply. Yale J. Biol. & Med. **22:** 251 (Jan.), 1950.

When the left branch of the pulmonary artery in the dog is ligated, blood from the bronchial arteries gains direct access to the capillaries of the alveoli through large precapillary anastomoses which develop with branches of the pulmonary arteries. These remain patent despite the ligature at the proximal end. As the collateral circulation expands, the bronchial vessels carry a much greater than normal flow. This places a severe load upon the left ventricle, since a situation analogous to an arteriovenous fistula exists, with the blood flowing from systemic artery to pulmonary vein.

The authors investigated the question of whether a lung deprived of its pulmonary arterial supply might still possess respiratory function. They found that the alveolar membranes were still permeable to gases, but that this permeability was impaired as compared with that of the normal lung.

ABRAMSON

PATHOLOGY

Tillett, W. S., and Sherry, S.: The Effect in Patients of Streptococcal Fibrinolysin (Streptokinase) and Streptococcal Desoxyribonuclease on Fibrinous, Purulent, and Sanguinous Pleural Exudations. J. Clin. Investigation **28:** 173 (Jan.), 1949.

A study of the enzymatic activities of the streptococcal products when introduced directly into the site of the disease, included 23 patients suffering from acute fibrinous pleurisy, bacterial empyema and hemothorax.

It was seen that through the mediation of substances elaborated by hemolytic streptococci, fibrin undergoes lysis, fibrinogen is altered so that it no longer assumes the solid form of fibrin, and the coarse sediment of purulent exudate (primarily desoxyribose nucleoprotein) is degraded to a thin solution. These substances were essentially nontoxic although febrile responses and local irritation were relatively common. The effects of these substances lasted several days and were self-limited.

The desirability of causing liquefaction of fibrin or preventing its formation or of resolving purulent sediments would depend on the conditions associated with the pathogenesis and expected evolution of the disease, for if the walling off process is advantageous, liquefaction of the wall might promote the spread of infection in its acute phases. On the other hand, the same walling off may prevent the introduction of antibacterial agents as well as antibiotic substances and, in these circumstances, elimination of the wall might be advantageous.

WAIFE

Plessinger, V. A., and Jolly, P. N.: Rasmussen's Aneurysms and Fatal Hemorrhage in Pulmonary Tuberculosis. Am. Rev. Tuberc. **60:** 589 (Nov.), 1949.

A series of 56 patients is presented, in 49 of whom death occurred as a result of massive pulmonary hemorrhage. These cases represent 7.2 per cent of 667 autopsies performed during a ten year period. The source of this hemorrhage was identified as a Rasmussen's aneurysm in 29 cases and a similar source of hemorrhage is postulated for the remainder. In 7 other cases, an unruptured Rasmussen's aneurysm was discovered as an incidental finding at autopsy.

These aneurysms and the resultant massive hemorrhages tended to occur in the more chronic forms of tuberculosis. The aneurysms consist of an aneurysmal dilatation of a branch of the pulmonary artery in a tuberculous cavity. In 10 of the 36 cases in which an aneurysm was found, the pulmonary artery was definitely identified as the site, and in another case the evidence pointed strongly to a similar source. About one-half which were identified occurred on the medial wall of the cavity.

It is believed that perivascular fibrosis aided in the formation of the aneurysm and also played a part in permitting massive hemorrhage to occur. Some factors may have temporarily or permanently controlled the bleeding, however: the fibrin clot; reduction of pressure and rate of flow in the pulmonary circuit; the tamponade effect of blood accumulating; and occasionally the clotting of the blood in the cavity and communicating bronchi. Several factors may have been instrumental in producing death as a result of pulmonary hemorrhage: suffocation from sudden aspiration of blood and obstruction of the bronchi; debilitation of sufficient degree that the effective clearing of the bronchi by coughing could not rake place; reflex laryngeal spasm from foreign material (blood) in the bronchi and trachea; and cerebral anoxemia.

BELLET

Haubrich, R., and Schuler, B.: Mercurial Embolism. Fortschr. a. d. Geb. d. Röntgenstrahlen. **72:** 68 (Nov.), 1949.

The authors describe the findings in a 25 year old woman who, while working on thermometers, developed a superficial abscess in her forearm. The abscess was treated expertantly at first and then was incised. Six weeks later the patient developed pulmonary symptoms and a roentgenogram showed numerous punctate metallic densities in both lower lung fields associated with pleural reaction at the left base. Analysis of her urine and stools indicated excretion of mercury by these routes. At this time too, accumulations of these fine dense deposition were noted within the right heart chambers. She died of pulmonary complications (miliary tuberculosis) within twenty-eight months of the onset of her arm abscess. At autopsy free mercurial particles were noted within the right ventricular myocardium as well as in the cavity.

SCHWEDEL

McMillan, G. C.: Diffuse Granulomatous Aortitis with Giant Cells, Associated with Partial Rupture and Dissection of the Aorta. Arch. Path. **49:** 63 (Jan.), 1950.

The author reports a case of diffuse granulomatous aortitis with partial rupture of the aorta, occurring in a 58 year old white man who was hypertensive and had a previous history of cerebellar hemorrhage. The Wassermann test was negative. Systemic blood pressure was 210/100. Death was caused by bronchopneumonia.

Necropsy showed left ventricular hypertrophy and a moderate sclerosis of the aorta. There was a longitudinal partially healed tear of the intima extending upwards from the posterior sinus of Valsalva; it did not extend through the full thickness of the wall. There was an associated thrombosis of the right internal carotid artery. Microscopy revealed in various regions of the aorta and in the left common iliac artery a focal destruction of the media, with a granulomatous reaction featured by vascularization and infiltration of large plasma cells, large mononuclear cells, and giant cells. The latter were both large and small. Some resembled typical Langhans cells; others were the common foreign body type. This inflammatory reaction was notable in and around the site of rupture of the aortic wall. Bacterial and Levaditi stains were negative.

Only seven cases of this lesion have previously been reported; this is the first with tear and dissection of the aortic wall. The similarity of the cellular infiltrations with those noted in temporal arteritis is pointed out. Although clinically there was no suggestion of temporal artery involvement, the author considers this case allied to temporal arteritis and to carotid arteritis, both of these conditions conceivably being variants of diffuse granulomatous giant cell arteritis.

GOULEY

PHARMACOLOGY

Binet, L., and Bernstein, M.: A Technic for Registration of Peripheral Vasomotor Reaction in the Rabbit. Vasoconstriction by Adrenalin and Histamine. Compt. rend. Soc. de biol. **143:** 915 (July), 1949.

A technic, previously developed for the dog, was applied in rabbits: a hind leg was perfused with the animal's own heparinized blood and pressures were recorded simultaneously in the carotid artery and the perfused vessel before and after injection of drugs into the afferent canula of the latter. Both adrenalin and histamine constricted the vessels in the perfused extremity of the rabbit. The vasoconstriction due to histamine was abolished by a synthetic antihistamine 3271 RP (Phenergan); however, this drug failed to abolish the vasodilatation produced by histamine in the dog.

PICK

Page, I. H.: Mechanism of the Vascular Action of Tetraethylammonium Chloride. Am. J. Physiol. **158:** 403 (Sept.), 1949.

In anesthesized dogs the blood pressure response to 5 to 10 mg. of tetraethylammonium chloride (TEA) was found to be inconstant, often consisting of pressor and depressor effects, and occasionally resulting in a distinct pressor response without depressor components. With considerable regularity

the pressure response following TEA administration was accentuated and the depressor effects diminished or abolished after lumbodorsal sympathectomy, cord destruction from C-6 caudad, and, less consistently, following bilateral nephrectomy. The depressor effect was enhanced and pressor responses partially or completely abolished by bilateral adrenalectomy, hepatectomy, and by adrenergic blocking agents (Dibenamine, Priscoline, Benzodioxane).

These observations are partially corroborated by experiments in cats and by clinical observations following the administration of TEA in man. They suggest that several factors are responsible for the changes in arterial pressure following the administration of TEA, some of which are concerned with (1) autonomic blockade, (2) liberation of a pressor substance of norepinephrine-like properties from the liver and (3) liberation of adrenalin from the adrenal gland.

HECHT

Wig, K. L., and Malhotra, R. P.: Streptomycin in Tuberculous Pericarditis. Indian Heart J. **1:** 254 (Sept.), 1949.

The authors report a case of pericarditis with a sanguinous pericardial effusion and a lesion in the right lung apex which they felt to be tuberculous in origin in spite of negative sputa as well as negative smears and cultures from the pericardial effusion. The patient was given streptomycin, 0.5 Gm. twice daily, about six weeks after the onset of his illness and he became afebrile seventeen days later. The pericardial effusion cleared about thirty days after starting streptomycin, though the lung lesion was still present. The authors feel that the streptomycin altered the course of this patient's illness.

BERNSTEIN

Das, A., and Chowduri, B. N.: Action of Nikethamide on Circulation and Respiration. Indian Heart J., **1:** 240 (Sept.), 1949.

In anesthetized cats Nikethamide in small doses had little action on the heart. In moderate to large doses it produced a decrease in cardiac output. It produced an initial fall of blood pressure in almost all animal experiments. The subsequent rise above normal level was practically absent. In humans Nikethamide produced neither a fall nor a rise of any significant degree. The authors found that Nikethamide acted as a powerful respiratory stimulant. In large doses it produced increased vasomotor irritability resulting in convulsive seizure.

BERNSTEIN

Arnold, P., Goetz, R. H., and Rosenheim, M. L.: Effect of Pentamethonium Iodide on the Peripheral Circulation. Lancet **2:** 408 (Sept.), 1949.

The effect of pentamethonium iodide upon the peripheral circulation was studied in 8 subjects by means of the digital plethysmograph. The intravenous administration of the drug produced a well-marked peripheral vasodilatation as a result of its blocking action on the paravertebral sympathetic ganglia; this effect was similar to that produced by tetraethylammonium chloride. It began within one minute of injection and persisted for at least one hour.

ABRAMSON

Schwartz, L., and Boger, W. P.: The Lack of Effect of Tween 80 on the Absorption of Aluminum and Sodium Penicillins. J. Lab. & Clin. Med. **34:** 1443 (Oct.), 1949.

The effect of Tween 80 (polyoxyethylene sorbitan monooleate) on the absorption of orally administered penicillin through the gastrointestinal tract was studied in 12 men. The results indicated that this drug did not enhance the absorption of the penicillin as determined by the penicillin plasma concentrations obtained.

ABRAMSON

Freis, E. D., Stanton, J. R., Litter, J., Culbertson, J. W., Halperin, M. H., Moister, F. C., and Wilkins, R. W.: The Hemodynamic Effects of Hypotensive Drugs in Man. II. Dihydroergocornine. J. Clin. Investigation **28:** 1387 (Nov.), 1949.

This article deals principally with hemodynamic responses after the intravenous injection of dihydroergocornine (DHO). The authors also studied the effects of DHO on renal blood flow, cardiac output, and the response to atropine and epinephrine. This synthetic alkaloid inhibited or abolished the vasopressor responses to the Valsalva maneuver, upright tilting, and the cold pressor test. Skin temperature in the digits increased in a warm environment but not in a cool environment. Changes in blood flow through the extremities and the hepatoportal circulation were not constant after the intravenous injection of DHO. Clinically, the studies suggested that the sympatholytic agents have certain fundamental limitations in the treatment of essential hypertension.

BUTTERWORTH

Schiff, L. F., and Schiff, L. J.: Anaphylactic Reaction to Intravenous Administration of Procaine. Anesthesiology **10:** 754 (Nov.), 1949.

A 74 year old hypertensive woman with arteriosclerotic peripheral vascular disease and an ulcer of the shin was given a course of intravenous 0.2 per cent procaine in saline because of refractoriness to other treatment. Usually 500 cc. of this solution were given over a period of one to one and one-half hours every second or third day. The thirteenth such infusion was complicated by the development of a mild chill and a slight attack of dyspnea which were attributed to a pyrogen reaction. The next infusion three days later was followed by severe dyspnea, wheezing and vasomotor collapse. Recov-

ery took place following epinephrine and Benadryl. An intradermal skin test with procaine two days later was negative. A month later, because of recurrence of severe pain, the usual infusion of procaine was given over the course of two hours. Following this the patient became dyspneic and quite confused mentally. Epinephrine produced good results but the patient required morphine for sedation. No further procaine was administered. These complications were attributed to an induced procaine sensitivity with subsequent anaphylactic shock.

KING

Moe, G. K., Rennick, B. R., Freyburger, W. A., and Malton, S. D.: The Effect of Cyclopropane on Cardiac Work Capacity. Anesthesiology **10:** 706 (Nov.), 1949.

Changes in auricular pressure were used as a measure of the heart's response to an increase in its work load. Variations in work load were accomplished in intact dogs by a pressure stabilizer attached to the abdominal aorta, and in dog heart-lung preparations by increasing either cardiac output or pressure loading. During exposure to cyclopropane, increased work load uniformly increased right auricular pressure in the intact dog and pressures in both auricles of the heart-lung preparation more than during control conditions with similar increases in work load. These increased auricular pressures were taken as an indication of a significant reduction of cardiac reserve apparent at cyclopropane concentrations of less than 15 per cent, and as an indication of a severe reduction at concentrations of 25 per cent to 35 per cent. These concentrations correspond to blood levels of 15 to 20 mg. per 100 cc. As a result of these findings the authors consider cyclopropane a possible hazard when used in patients with cardiac disease.

KING

Krayer, O., and Van Maanen, E. F.: Studies on Veratrum Alkaloids. X. The Inhibition by Veratramine of the Positive Chronotropic Effect of Accelerans Stimulation and of Norepinephrine. J. Pharmacol. & Exper. Therap. **97:** 301 (Nov.), 1949.

Veratramine's mode of action in inhibiting the cardioaccelerator action of epinephrine was investigated in intact cats and dogs. In a dose of 0.1 to 0.2 mg. per Kg. intravenously, veratramine inhibits the cardioaccelerator action of electrical stimulation of the accelerans nerve. Likewise the accelerator action of l-norepinephrine as well as that of l-epinephrine is inhibited. Since l-norepinephrine and l-epinephrine are presumably involved in the transmission of impulses from the accelerans nerves to the pacemaker tissue, veratramine presumably blocks the pacemaker tissue against sympathomimetic amines.

GODFREY

Krayer, O.: Studies on Veratrum Alkaloids. IX. The Inhibition by Veratrosine of the Cardioaccelerator Action of Epinephrine and of Norepinephrine. J. Pharmacol. & Exper. Therap. **97:** 256 (Nov.), 1949.

Veratramine, a veratrum alkaloid, has recently been shown to antagonize the cardioaccelerator action of epinephrine. This has led to the investigation of several related alkaloids. Veratrosine is an alkaloid isolated from veratrum viride which, on hydrolysis, splits into veratramine and d-glucose. The inhibition of cardiac acceleration by veratrosine was studied in the heart-lung preparation of the dog, in intact anesthetized dogs and cats, and in pithed cats. In most preparations epinephrine was given by continuous infusion and the veratrosine administered in one or more single injections. Veratrosine was found to inhibit the cardioacceleration induced by epinephrine; however, this action was not rapid like that of veratramine but appeared after fifteen to fifty minutes in various preparations. The vasopresser action of epinephrine was not influenced by amounts of the drug sufficient to inhibit cardiac acceleration; likewise restoration of competence in experimental failure by epinephrine was not inhibited although acceleration was abolished. The action of veratrosine is believed to be in the pacemaker tissue of the heart and is not modified by atropine.

GODFREY

Nyman, E.: Does Human Blood Contain Appreciable Amounts of Atropinesterase? Acta med. Scandinav. **136:** 9 (Nov.), 1949.

The widespread clinical use of the belladonna alkaloids and the varying tolerance of human subjects to these substances raises the question of whether human blood contains any atropinesterase activity primarily or whether such a factor can be acquired. A number of investigators have studied the specificity of the enzyme, which is quite different from cholinesterase, and have found varying amounts in dogs, cats, rats and rabbits.

The author examined the blood of 288 humans for atropinesterase activity by mixing their sera or plasma with atropine or the methonitrate of scopolamine and measuring the mydriatic effect of the mixture when injected subcutaneously into white mice. In none of the 288 cases, including normal individuals, pregnant women, individuals with various diseases and a series of patients treated over an extensive period with massive doses of atropine, was any evidence found of the presence of atropinesterase activity. The author concludes that it is very unlikely that human blood contains any appreciable power of destroying atropine or quaternary bases of the atropine group.

SCHWARTZ

Latterell, K. E., and Lundy, J. S.: Oxygen and Carbon Dioxide Content of Arterial Blood Before

and During Spinal Analgesia. Anesthesiology **10:** 677 (Nov.), 1949.

The effects of spinal anesthesia on arterial oxygen saturation were followed continuously (by means of the Millikan oximeter) in 25 patients during operation. Corrections in the oximeter readings were made by arterial blood samples analyzed by the method of Van Slyke. All patients received routine preoperative premedication of morphine, atropine and pentobarbital, and also a prophylactic pressor drug. The changes in saturation were relatively small; the maximal decrease was 9 per cent, with the average change in all cases a decrease of 1 per cent. The average of the lowest oxygen saturations reached was 93.6 per cent. Paralysis of intercostal nerves produced by the anesthesia was believed to be compensated for by increased diaphragmatic excursions, although no measurements of respiratory minute volume were made. Nausea which occurred in some cases was not found to be associated with a decrease in arterial oxygen saturation. During spinal anesthesia the blood carbon dioxide was found to be within normal limits.

KING

Barcroft, H., and Konzett, H.: On the Actions of Noradrenaline, Adrenaline, and Isopropyl Noradrenaline on the Arterial Blood Pressure, Heart Rate, and Muscle Blood Flow in Man. J. Physiol. **110:** 194 (Dec.), 1949.

Noradrenaline causes (1) constriction of the cutaneous vessels; (2) constriction of the vessels in skeletal muscle (adrenaline causes transient vasodilatation); (3) bradycardia (adrenaline causes tachycardia); (4) rise in both systolic and diastolic pressures (adrenaline causes a rise in systolic pressure and either does not affect or causes a slight fall in diastolic pressure). Isopropyl adrenaline results in (1) dilatation of the vessels in the skin; (2) transient dilatation of the vessels in skeletal muscle; (3) persistent tachycardia; and (4) a rise in systolic and a marked fall in diastolic blood pressures.

WHITE

Grace, A. W., and Combes, F. C.: Remission of Disseminated Lupus Erythematosus Induced by Adrenocorticotropin. Proc. Soc. Exper. Biol. & Med. **72:** 563 (Dec.), 1949.

This report describes the effect of pituitary adrenocorticotropic hormone (ACTH) in inducing three temporary dramatic remissions in 2 patients with classic disseminated lupus erythematosus. In each case, there was temporary, striking clinical improvement and fading of the skin lesions, accompanied by the expected signs of increased adrenal cortical activity. There was almost complete clinical remission while the ACTH was being administered.

It appears likely that the hormones ACTH and Compound E (Kendall) only inhibit or mask the peripheral manifestations of rheumatoid arthritis, rheumatic fever, lupus erythematosus and psoriasis and do not effect the underlying causative disease mechanism, since a clinical relapse usually occurs promptly after cessation of the hormone treatment. In acute gouty arthritis, on the other hand, ACTH apparently aborts the acute attack.

There are none of the usual signs or symptoms of adrenal insufficiency in the diseases benefited by ACTH or Compound E, and it is unlikely that the hormones act as substitution therapy for a deficiency. The expected change in the ketosteroids, eosinophils, lymphocytes and total white blood cell count is evidence for adequate adrenal cortical function. A "pharmacologic" extension of the usual physiologic properties of the hormones may be responsible for their action. It is interesting to note the similarities between the effects produced by the salicylates and the adrenal hormone. The salicylates and adrenal hormones lower fever and sedimentation rate, inhibit hyaluronidase, cause hyperglycemia, increase uric acid excretion, are local anesthetics and are effective in the treatment of rheumatoid arthritis and lupus erythematosus.

MINTZ

PHYSIOLOGY

De Meyer, R.: Contribution to the Study of the Specific Muscle System of the Heart in Birds. Compt. rend. Soc. de biol. **143:** 992 (July), 1949.

The distribution of the specific muscle system in the auricles of the heart of the sparrow resembles in general the distribution in the human heart; however, a structure in the sparrow heart similar to the node of Aschoff-Twara is variable in development and localization. In the examined heart of a young sparrow neither a sinus node nor an A-V node could be identified. It seems probable that the development of these structures in the species studied depends on the age of the bird. Certain structures may appear early and disappear later while others are differentiated only in a later stage of development.

PICK

Ebert, R. V., Borden, C. W., Wells, H. S., and Wilson, R. H.: Studies of the Pulmonary Circulation. I. Circulation Time from the Pulmonary Artery to the Femoral Artery and the Quantity of Blood in the Lungs in Normal Individuals. J. Clin. Investigation **28:** 1134 (Sept.), 1949.

The authors studied the pulmonary circulation in 12 normal male subjects by injecting a dye (T-1824) into the pulmonary artery through an intracardiac catheter and determining the concentration of the dye in consecutive samples of blood from the femoral artery. Using cardiac output values determined by the direct Fick method at the same time, it is theoretically possible to measure the quantity of blood

within the lungs. The mean pulmonary-femoral artery circulation time was 10.2 ± 1.6 seconds. The average blood volume of the pulmonary vessels, left heart, aorta and iliac arteries, together with all the blood in other aortic branches to points where dye arrives no later than it does at the femoral artery, was 1160 ± 246 cc. This was 19.5 per cent of the total blood volume.

WAIFE

Selkurt, E. E., Hall, P. W., and Spencer, M. P.: Influence of Graded Arterial Pressure Decrement on Renal Clearance of Creatinine, p-Aminohippurate and Sodium. Am. J. Physiol. **159:** 369 (Nov.), 1949.

The effect of graded decrease in arterial blood pressure on renal blood flow, glomerular filtration rate and sodium excretion was studied in dogs. The inflow pressure to the left kidney was reduced in stepwise fashion by aortic occlusion, while the mean arterial pressure in the right kidney was maintained and served as a control. It was found that in the earlier stages of decreased arterial pressure, the renal clearances are maintained, but these soon decrease as mean arterial pressure continues to fall below 100 mm. Hg. There is an afferent dilatation, presumably to compensate for the decrease in driving force. This intrarenal adjustment is a buffering mechanism against falls in systemic arterial pressure. When the glomerular filtration falls, and the load of sodium presented to the tubules is decreased, there is a more complete reabsorption leading to a decreased excretion of sodium. This mechanism of decreased sodium excretion with decreased glomerular filtration rate may be involved in congestive failure.

MOKOTOFF

Stevenson, I. I., Duncan, C. H., and Wolff, H. G.: Circulatory Dynamics before and after Exercise in Subjects with and without Structural Heart Disease during Anxiety and Relaxation. J. Clin. Investigation **28:** 1534 (Nov.), 1949.

The authors measured the heart rate, stroke volume and blood pressure (cardiac index and peripheral resistance were calculated) before and after standard exercise in a group of subjects without heart disease. These subjects were divided into groups consisting of (1) subjects able to achieve complete relaxation during the test; (2) subjects who were preoccupied; and (3) subjects who had marked conscious anxiety. Other patients with structural heart disease or hypertension were also studied.

It was found that in both normal and structurally altered hearts the cardiac outputs, both before and after exercise, were greater in the group of persons slightly disturbed emotionally than in the apparently relaxed group, and in turn the output of the marked anxiety group was greater than that of any of the other groups. There was a close correlation between symptoms of effort intolerance and impaired exercise tolerance in both normal and structurally altered hearts.

The authors feel that impaired exercise tolerance during emotional disturbances results from exaggerated cardiac mobilization in response to stimuli to action. In early stages increased output is mainly achieved by increase in stroke volume. They also feel that ordinary physical exertion during periods of relaxation imposes little extra work on the heart compared with the cardiac mobilization associated with anxiety, and they feel that the increased cardiac work during anxiety may be relevant to the increased susceptibility of patients with tachycardia to the development of structural heart disease.

BUTTERWORTH

Fabricius, B.: Combined Kymographic and Electrocardiographic Studies of the Duration of the Presphygmic Period. Acta med. Scandinav. **136:** 34 (Nov.), 1949.

The presphygmic period is the period of time in cardiac systole between the closure of the atrioventricular valves and the opening of the semilunar valves. Its duration is usually determined by taking electrocardiograms and pulse curves simultaneously. The author measured this period by a method combining simultaneous electrocardiography and kymography, using a 36 mm. grid diaphragm. The duration of the presphygmic period was calculated to be equal to the time-interval between the beginning of the QRS complex and that of the lateral movement of the aorta plus or minus the length of time the mitral valve closure notch on the ventricular border occurs before or after the QRS complex. In an examination of 22 young normal subjects the length of the presphygmic period was found to be 0.02 second in one case, and 0.03 second in another, but otherwise it varied between 0.04 and 0.08 second, with an average value of 0.06 second.

SCHWARTZ

Bruce, R. A., Pearson, R., Lovejoy, F. W., Jr., Yu, P. N. G., and Brothers, G. B.: Variability of Respiratory and Circulatory Performance during Standardized Exercise. J. Clin. Investigation **28:** 1431 (Nov.), 1949.

This paper is a statistical analysis of the cardiorespiratory performance of 35 normal adults in a standardized exercise test. It was found that the average coefficient of variability for blood pressure, arterial oxygen saturation, precordial electrocardiogram, ventilation volume, expired gases and respiratory rate, observed and measured during rest, exercise and recovery, was about 12 per cent. However, analyses of data from multiple tests on the same individual, whether a normal subject or a patient with clinical disease, showed average coefficients of variability of about 5 per cent and 10 per cent, respectively.

BUTTERWORTH

Remington, J. W., Hamilton, W. F., Wheeler, N. C., and Hamilton, W. F., Jr.: Validity of Pulse Contour Method for Calculating Cardiac Output of the Dog, with Notes on Effect of Various Anesthetics. Am. J. Physiol. **159:** 379 (Nov.), 1949.

The authors used a modified procedure for calculating the stroke index of the dog from the aortic pressure pulse contour. In 187 instances this method was within ± 10.1 per cent of the value obtained by the direct Fick or the simultaneous dye injection technique. The contour method was accurate within a mean pressure range of 23 to 300 millimeters of mercury.

MOKOTOFF

Mackay, I. F. S., and Pickles, V. R.: Volume Changes in Forearm and Hand following Release of Obstruction to Venous Return. J. Applied Physiol. **2:** 261 (Nov.), 1949.

Changes observed in limb volume after release of a venous occlusion pressure were studied in 13 subjects by means of a plethysmograph. The first alteration was a decrease in volume which was not dependent upon arterial inflow but rather upon the recovery of the large veins from the distending force. When this occurred, there was a rapid ejection of blood from the limb. Following the initial drop there was an increase in volume and then a secondary decrement as the limb volume gradually returned to normal.

ABRAMSON

Mills, J. N.: Variability of the Vital Capacity of the Normal Human Subject. J. Physiol. **110:** 76 (Dec.), 1949.

Variations of the vital capacity of the normal human subject under supposedly identical conditions were studied in 17 healthy men. The author found that in any one subject and upon any one occasion, the values are normally distributed, and the standard deviation usually lies between 50 and 200 cc. Variance analysis shows a considerable day to day variation in the vital capacity outside the variation to be expected on one occasion. In one subject the vital capacity increased about one liter.

WHITE

Mills, J. N.: The Influence of Abdominal Distention upon the Vital Capacity. J. Physiol. **110:** 83 (Dec.), 1949.

The vital capacity shows small, inconstant changes upon addition of 1 liter of water or 1 kilogram food to the empty stomach, but usually falls slightly upon addition of a second liter and rises slightly when the stomach is drained. One liter of extra fluid in the stomach neither restricts inspiration nor assists expiration.

WHITE

Schneierson, S. J., and Krainin, P.: Visualization of Skin Veins with the Use of Dark-Adaptor Glasses. Ann. Int. Med. **32:** 120 (Jan.), 1950.

The dark-adaptor goggles which are usually worn by the examiner prior to fluoroscopy provide a simple aid for the inspection of superficial veins in the integument of the body. The dark-adaptor glasses filter out the blue rays reflected from the blood in the veins, and, as a result, such veins appear as very dark structures. The use of the dark-adaptor goggles also enables more satisfactory determination of the direction of blood flow. Thus, in obstruction of the superior vena cava, one looks for collateral veins on the chest wall. In such an instance, using dark-adaptor goggles, one can visualize small superficial venous collaterals not readily seen by the naked eye. In addition, one may more readily determine the direction of blood flow in these veins. If the current is from above downward evidence is strong that obstruction of the superior vena cava exists. In obstruction of the innominate vein better visualization of small venous patterns and the direction of blood flow within them may disclose unilateral venous collaterals of the integument which might otherwise be overlooked.

WENDKOS

Ellis, E. J., Gauer, O., and Wood, E. H.: Application of a Manometric Sound to the Recording of Intracardiac and Intravascular Pressures. Proc. Staff Meet., Mayo Clin. **25:** 49 (Feb.), 1950.

The usual method of recording pressure during cardiac catheterization employs one of various manometers such as the Hamilton manometer, the resistance-wire strain-gauge manometer or various capacitance manometers that record from the external end of the catheter. Although reasonably accurate manometer–catheter systems can be evolved by testing with sine wave pressure oscillators and square wave or step response methods, there are inherent physical difficulties which distort the recorded pulse. The most important of these is the artefact produced by the acceleration and deceleration of the fluid contained within the catheter, caused by movement of the catheter due to the heart beat. An intracardiac manometer has been developed by one of the authors (O. Gauer) which creates a pressure transducer by utilizing the variation in inductance produced between two miniature transformers. The head or end of the actual manometer containing the transformers is only slightly larger than an 8F cardiac catheter and projects 1.2 cm. beyond the woven tip. The instrument will record accurately well beyond the range necessary to reproduce the normal central pulse. A comparison between the tracings obtained with the strain-gauge manometer–catheter system and the new instrument demonstrates the more accurate artefact-free recording of blood pressure during cardiac catheterization when using the latter.

SIMON

Cooper, K. E., Cross, K. W., Greenfield, A. D. M., McK. Hamilton, D., and Scarborough, H.: A Comparison of Methods for Gaging the Blood Flow through the Hand. Clin. Sc. **8:** 217, 1949.

A comparison was made of the results obtained with various methods of studying blood flow in the hand. When compared over periods of time, the arterial inflow, as measured by the venous occlusion plethysmographic method, was quite similar to the inflow as determined by the Stewart's calorimeter, which measures heat elimination. The plethysmograph recorded rapid changes in circulation while the calorimeter picked up these alterations much more slowly. Skin temperature responded promptly to increases in blood flow but it fell slowly when the circulation was abruptly reduced or arrested.

ABRAMSON

Werke, L., Lagerlof, H., Bucht, B., Wehle, B., and Holmgren, A.: Comparison of the Fick and Hamilton methods for the determination of cardiac output in man. Scandinav. J. Clin. & Lab. Investigation **1:** 109 (No. 2), 1949.

Simultaneous determinations of the cardiac output by the dye injection method and by the direct Fick method were made 69 times in 50 cases. Results of this study indicated that there is no systematic difference between the direct Fick and the dye injection principle for determination of cardiac output in man. Calculations indicated that the errors of both methods of determining cardiac output are of the same order of magnitude, amounting to about 11 per cent. Since the dye injection method covers the cardiac output for, at most, ten seconds, it is possible that the resultant values are influenced by the phases of respiration, whereas the Fick values necessarily represent the mean cardiac output during the respiratory cycles.

In the technique used by the authors, blood samples for both methods were taken within two minutes, thereby reducing the possibility of a shift in the basal state of the patient. Injection of the dye into the pulmonary artery resulted in a dilution curve that almost approached zero in most cases before recirculation occurred, thus making the amount of necessary extrapolation small and unimportant.

SCHWARTZ

RHEUMATIC FEVER

Suarez, G.: Carditis: Simple Rheumatic, Evolving, and Malignant Forms are the Same Illness. Arch. enferm. corazon y vasos **46:** 5 (July), 1949.

The author expresses his belief that rheumatism is not the etiological agent for the frequently associated valvular heart disease. The association of the terms "rheumatic" and "endocarditis" or "carditis" is unwarranted. He states that rheumatic fever in all of its manifestations and carditis are both due to an indolent infection from septic foci. He denies that a fresh vegetative malignant lesion is superimposed on a previously healed valvular lesion. Endocarditis and carditis, in his opinion, begin as bacterial involvement, either direct or as an allergic response, evolve through stages of recurrences, and finally, lacking immunity, result in the frank bacterial forms. He prefers the use of the term "carditis, nodular, bacteriofocal, relapsing" to other terms. The author refers to his recently published book "Rheumatic Carditis" for data on autovaccine immunization which he states has averted recurrences for as long as six to eighteen years.

SCHWEDEL

Heyer, H. E., Hansen, A. E., Chapman, D. W., Adamson, W. B., and Parsons, G. W.: Deaths from Acute Rheumatic Fever in Texas: Relationship to Mean January Temperature. Am. J. M. Sc. **219:** 40 (Jan.), 1950.

The results of this study indicate that the mortality rate for acute rheumatic fever is higher in those areas of Texas that are subject to fairly cold winters than in counties with mild winters. From this survey alone it was impossible to determine whether the increased rate in the former was due to increased severity, or to increased prevalence, or to both. It is assumed, however, that both are involved.

The exact manner in which a cold climate could produce an increase in either the prevalence or the severity of the disease is still probably unknown. It seems possible that climate might exert its effects either by facilitating the transfer of streptococci and possibly increasing their virulence, or by affecting the host.

DURANT

ROENTGENOLOGY

Kohler, L. M.: Apparent Cardiac Enlargement in the Roentgenogram of Funnel Chest. Fortschr. a. d. Geb. d. Roentgenstrahlen **71:** 548 (Aug.), 1949.

The author discusses eight instances of funnel chest deformity where the sternovertebral depth had been greatly reduced. This chest deformity resulted in abnormal widening of the heart shadow in the posteroanterior position in all instances. Usually there also was some displacement of the heart into the left chest. In the lateral projection the heart depth was diminished. It seemed that the depth of the heart diminished as heart width increased.

SCHWEDEL

Kaisch, A. M.: Clinical and Roentgenologic Aspects of Esophageal Lesions in Scleroderma. Report of Six Cases. Am. J. Digest. Dis. **16:** 405 (Nov.), 1949.

The author presents 6 cases to emphasize the oc-

currence of esophageal lesions in scleroderma and to stress the clinical and roentgen findings. The characteristic pathologic findings in scleroderma are proliferation of the connective tissue stroma leading to rupture and disappearance of elastic fibers and alterations in the small blood vessels. Very few patients go through the course of the disease without some gastrointestinal disturbance. All of the 6 cases reported had demonstrable esophageal lesions, 5 on roentgen examination and 1 on postmortem study. Dyspeptic symptoms and dysphagia are characteristic when the esophagus is involved. Roentgenologically, there may be diffuse dilatation of the entire esophagus or dilatation may occur proximal to an area of stricture. Peristalsis is much diminished or entirely absent. Scleroderma of the esophagus may be confused with phrenic ampulla or cardiospasm but may be differentiated by the roentgenologic appearance.

SCHWARTZ

Steinberg, I., Dotter, C. T., and Andrus, W. DeW.: Angiocardiography in Thoracic Surgery. Surg., Gynec. & Obst. **90:** 45 (Jan.), 1950.

The authors discuss the application of the angiocardiographic method to the diagnosis and to the planning of the surgical attack on mediastinal and pulmonary lesions. The successful extirpation of a mediastinal tumor depends on its separation from large vessels or parts of the heart with which it may be in intimate contact. Knowledge of such relationships may avert hemorrhage secondary to accidental entry into vessels or atria.

Illustrative examples are given of aortic aneurysm simulating mediastinal tumor; mediastinal dermoid cyst containing calcium at its border; pericardial cyst; bronchogenic cyst displacing the trachea to the right; a calcium-rimmed thymoma; lymphoma with stenosis of the subclavian and innominate veins and occlusion of the superior vena cava resulting in collateral venous circulation; bronchogenic carcinoma narrowing and distorting the left pulmonary artery; pulmonary tuberculous lesion simulating bronchogenic carcinoma; and bronciectasis.

SCHWEDEL

SURGERY IN HEART AND VASCULAR SYSTEM

Cossio, P., and Perretta, A.: Inferior Cava Ligation and Edema of the Legs. Rev. argent. de cardiol. **16:** 293 (Sept.–Oct.), 1949.

Ligation of the inferior cava in 71 patients, and of other veins in 4 patients was done for relief of recurrent pulmonary edema due to cardiac failure. Twenty-three and one-half per cent of the patients having no edema of the legs before surgery presented edema within the first two weeks; 3:9 per cent presented edema at a later date. Edema of early onset was usually transient and predominant on the right side; it was accompanied by painful swelling at the groin and, occasionally, fever. Edema of late occurrence was usually concomitant with a recurrence of cardiac failure. Edema of early onset is attributed to lymphatic block and inflammatory reaction. Edema of late onset is explained by a more difficult lymphatic circulation on account of high pressure in the superior cava. Sixty per cent of the patients having edema of the legs prior to surgery reabsorbed the edema after inferior cava ligation. This is explained by a more effective lymphatic drainage secondary to diminution of venous pressure in the superior cava. The importance of disturbances of the lymphatic circulation in the production of peripheral edema is emphasized.

LUISADA

Koppermann, E.: Concretio Pericardii, Hemodynamics of Four Cases before and after Pericardectomy. Ztschr. f. Kreislaufforsch. **38:** 598 (Oct.), 1949.

The evaluation of cardiodynamics by the method of Wezler and Boeger gave indications for pericardiectomy in 4 out of 5 patients with constrictive pericarditis. Reexamination after operation showed no improvement. The cardiac output and minute volume remained low and the electrocardiogram and functional capacity remained unchanged. In 2 of the patients a second operation was required after 8 months and 11 years, respectively; a third patient died two months after operation in congestive heart failure.

PICK

Collins, C. G., Nelson, E. W., Ray, C. T., Weinstein, B. B., and Collins, J. H.: Ligation of the Vena Cava and Ovarian Vessels. Am. J. Obst. & Gynec. **58:** 1155 (Dec.), 1949.

The authors present the results of ligation of the inferior vena cava and ovarian vessels in 59 patients who suffered from acute suppurative pelvic thrombophlebitis. In some of the patients the operation was performed because they had failed to improve after four or five days of medical treatment, while in others pulmonary infarction had already occurred. All but 7 patients survived the operation. Immediately following ligation, mild edema of the legs and ankles was noted in most cases, but this disappeared completely within a few weeks or months except in 9 instances. The fact that in nearly all the cases the lumbar sympathetic chains were severed at the time of ligation was held responsible for the lack of arterial spasm generally associated with ligation of a large venous trunk. On the basis of various physiologic observations, it was felt that adequate vascular compensations developed following vena caval ligation.

ABRAMSON

Vineberg, A. M.: Development of Anastomosis between the Coronary Vessels and a Transplanted

Internal Mammary Artery. J. Thoracic Surg. **18:** 839 (Dec.), 1949.

The basic objective of this work was to supply a fresh source of arterial blood to the heart muscles. In order to do this, the left internal mammary artery was partially removed from its normal position on the chest wall and implanted into the myocardium of the left ventricle. All operations were performed on dogs who were kept under observation from six weeks to thirteen months. The presence of anastomosis between a transplanted left internal mammary artery and the left coronary circulation was studied by means of (1) x-ray examination of injected specimens; (2) serial sections taken through the site of anastomosis; and (3) a plastic cast of the arteries involved to show the nature of anastomosis. Certain technical difficulties which were encountered in the dog should not be met with in man. The left internal mammary artery, after implantation into the left ventricular wall, formed a communication with the circulation of the left coronary vessels.

BECK

THROMBOEMBOLIC PHENOMENA

Abizanda, J. M.: Migratory Phlebitis. Arch. enferm. corazon y vasos **46:** 9 (July), 1949.

The author states that migratory phlebitis may precede thromboangiitis in from 10 to 40 per cent of instances. It may manifest itself in the venous or nodular forms in thickened palpable vessels, or as regional enlargement of an extremity without evident edema or venous localization. Phlebitis migrans is superficial, devoid of fever and leukocytosis, and is not accompanied by edema which differentiates it from deeper forms of thrombophlebitis. Biopsy is often helpful in showing local venous obliteration by thrombus with perivascular, polynuclear, lymphocytic and plasma cell infiltration. The author cites an illustrative case of superficial thrombomigratory phlebitis in a young man who had no subjective or objective alteration of the arterial circulation except for diminished oscillometric pulsations which subsequently improved with paravertebral novocaine block and then ganglionectomy.

SCHWEDEL

AMERICAN HEART ASSOCIATION, INC.

1775 BROADWAY, NEW YORK 19, N. Y.

Telephone Plaza 7-2045

"YOU AND YOUR HEART"

Questions frequently asked by patients about their hearts and heart disease are answered in a nontechnical book for the lay public, "You and Your Heart," just published by Random House ($3.00). The book is written by Dr. H. M. Marvin, President of the American Heart Association, and four other specialists in the field.

The book is intended to satisfy the desire of "many intelligent healthy people to know more about their own hearts, to understand more clearly the causes of heart diseases, their significance and frequency, the progress that has been made in this field, and the hopes for the future. For those who have heart disease, it explains more fully some of the reasons for the treatments prescribed, the instructions given, and the limitations imposed, by their doctors."

Special chapters have been contributed by Dr. T. Duckett Jones, Medical Director of the Helen Hay Whitney Foundation; Dr. Irvine H. Page, Director of Research, Cleveland Clinic Foundation and Chairman of the Medical Advisory Board, Council for High Blood Pressure Research of the Association; Dr. Irving S. Wright, President, New York Heart Association, and Professor of Clinical Medicine, Cornell University; and Dr. David D. Rutstein, Professor of Preventive Medicine, Harvard University. Dr. Paul D. White, former President of the Association, has written a Foreword.

Copies of "You and Your Heart" may be ordered through local heart associations or from the American Heart Association in New York.

LEGION PENICILLIN GIFT

The American Legion has made the Association a gift of 960 million units of penicillin which was donated by Legion Post 111, Department of New York. The Research Study Committee of the American Council on Rheu-

matic Fever has recommended that this penicillin be used in a prophylaxis program for rheumatic fever.

ARTERIOSCLEROSIS

The Annual Meeting of the American Society for the Study of Arteriosclerosis will be held at the Knickerbocker Hotel, Chicago, November 5th and 6th, 1950. Contributions to the scientific program are invited. Titles and abstracts (not exceeding 200 words) should be sent not later than June 15th, 1950, to Dr. G. Lyman Duff, Chairman of the Program Committee, 3775 University Street, Montreal, Canada.

ANNUAL MEETING

The Annual Dinner of the Association will be held at the Fairmont Hotel, San Francisco, on Saturday, June 24, 1950, at 7:30 P.M. Members are reminded to send in their reservations as early as possible.

The Scientific Sessions will be held Thursday, June 22, to Saturday, June 24. Assembly meetings are scheduled for the afternoon of Saturday, June 24, and the morning of Sunday, June 25. A Board of Directors Meeting will be held on the afternoon of June 25.

SCIENTIFIC SESSIONS

Following is a complete program of the Twenty-third Scientific Sessions to be held at the Association's Annual Meeting in the Gold Room of the hotel.

First Session: 1:30 P.M., Thursday, June 22

Chairman: Hugh McCulloch, American Council on Rheumatic Fever

1. *Staphylococcus Bacterial Endocarditis—A Report of 18 Cases with Observations on Bacterial Resistance*, David C. Levinson, Harold D. Anderson and George C. Griffith, Los Angeles.

2. *Prevention of Rheumatic Fever by Prompt Penicillin Therapy of Hemolytic Streptococcal Respiratory Infections*, Benedict F. Massell, George P. Sturgis, Richard B. Streeper, Thomas N. Hall, Joseph D. Knobloch and Pliny Norcross, Boston.

3. *Mural Thrombosis and Arterial Embolism in Mitral Stenosis: A Clinicopathologic Analysis of 51 Cases*, Robert A. Jordan, Charles H. Scheifley and Jesse E. Edwards, Rochester, Minn.

4. *Electrokymography in the Diagnosis of Chronic Constrictive Pericarditis*, Victor A. McKusick, Baltimore

5. *The Nature of Auricular Flutter in Man*, Myron Prinzmetal, Eliot Corday, Robert Oblath, Isidor C. Brill and H. E. Kruger, Los Angeles

6. Lewis A. Conner Memorial Lecture—*The Present Status of Treatment of Subacute Bacterial Endocarditis*, Arthur L. Bloomfield, San Francisco

7. *The Effects of Cortisone and ACTH on Periarteritis Nodosa and Cranial Arteritis: Preliminary Report*, Richard M. Shick, Archie H. Baggenstoss and Howard F. Polley, Rochester, Minn.

8. *The Effect of Adrenocorticotrophic Hormone (ACTH) on Rheumatic Fever*, Albert Dorfman, Delbert M. Bergenstal, Earl P. Benditt and Frances E. Moses, Chicago

9. *The Response of the Hyaluronidase Inhibitor and Mucoproteins in ACTH Therapy of Rheumatic States*, Forrest H. Adams, Vincent C. Kelley, Paul F. Dwan and David Glick, Minneapolis.

10. *The Effect of ACTH and Cortisone on Rheumatic Fever*, Joseph J. Bunim, Currier McEwen, Janet S. Baldwin and Ann G. Kuttner, New York.

Panel Discussion: Rheumatic Fever.

Second Session: 9:00 A.M., Friday, June 23

Chairman: Robert W. Wilkins, Section on Circulation

11. *The Effects of Bleeding on Sodium Excretion, Cardiac Output, and Glomerular Filtration of Normal Subjects*, Seymour Eisenberg, B. B. Oliver, Tom Lombardo and William Viar, Dallas.

12. *Comparison of Reactive Hyperemia with Other Vasodilating Procedures for Determining the Functional Capacity of the Peripheral Circulation*, Travis Winsor, Los Angeles

13. *A New Humoral Pressor Substance Present in Arterial Hypertension*, Henry A. Schroeder and Norman S. Olsen, St. Louis

14. *The Relationship Between the Nature of Cholesterol Transport and The Development of Atherosclerosis*, John W. Gofman, Thomas P. Lyon, Frank Lindgren, Hardin B. Jones and Harold Elliott, Berkeley.

15. George E. Brown Memorial Lecture—*Scientific Research is Progress*, Edgar V. Allen, Rochester, Minn.

16. *Oxygen Tension and Blood Flow of the Skin of Normal and Ischemic Human Extremities*, Hugh Montgomery and Orville Horwitz, Philadelphia

17. *Controlled Observations on Low-Sodium Diet-therapy of Essential Hypertension*, A. C. Corcoran, R. D. Taylor and Irvine H. Page, Cleveland

18. *A Clinical Method of Estimating the Blood Pressure in the Subpapillary Plexus of the Human Extremity by the Method of Elevation and Reactive Hyperemia*, Rutherford S. Gilfillan and Norman E. Freeman, San Francisco

19. *The Measurement of Peripheral Resistance in Man*, Milton Mendlowitz, New York

PANEL DISCUSSION: Hypertension.

Third Session: 1:30 P.M., Friday, June 23

Chairman: H. M. Marvin, President, American Heart Association.

20. *The Urinary and Biliary Excretion of Digitoxin in the Normal and Cardiac Patient*, Meyer Friedman, René Bine, Jr. and Sanford O. Byers, San Francisco

21. *Physiological Demonstration of the Blocking Action of Atropine and the Antihistaminic Drugs on Coronary Artery Vasoconstriction*, Durwood J. Smith and Joseph W. Coxe, Rochester, N. Y.

22. *Procaine Amide in the Treatment of Cardiac Arrhythmias*, Herbert J. Kayden, Lester C. Mark, J. Murray Steele and Bernard B. Brodie, New York

23. *Comparison of Cardiorespiratory Performance in Patients with Diseases of the Heart and Lungs, and Normal Subjects under Unusual Stresses during Exercise*, Robert A. Bruce, Frank W. Lovejoy, Paul N. G. Yu, Marion E. McDowell and William S. McCann, Rochester, N. Y.

24. *The Action of Strophanthus K. on the Coronary Circulation and Cardiac Oxygen Consumption of the Normal and Failing Heart in vivo*, R. J. Bing, F. Maraist, J. Jacobs, R. Heimbecker, I. R. Goldman, A. Draper and J. F. Dammann, Jr., Baltimore

25. *Programs of the Public Health Service in the Attack on Cardiovascular Diseases*, Leonard A. Scheele, Washington

26. *Vibrations of Low Frequency Over the Precordium*, Franklin D. Johnston, Ann Arbor, Mich.

27. *Experimental and Clinical Experiences with the New Anticoagulants—Tromexan and Paritol*, Irving S. Wright, C. W. Sorenson and Grafton Burke, New York

28. *Experimental Studies on Therapy of Acute Pulmonary Edema*, Aldo A. Luisada, Chicago

29. *Treatment of Congestive Heart Failure with 50 mg. Sodium Diet—Metabolic and Clinical Study*, Lloyd T. Iseri, Albert J. Boyle and Gordon B. Myers, Detroit

PANEL DISCUSSION: Modern Treatment of Cardiovascular Diseases.

5:30 P.M., Friday, June 23

Annual Business Meeting.

Fourth Session: 9:00 A.M., Saturday, June 24

Chairman: Louise Martin, Chairman, Program Committee

30. *The Electrocardiogram in Congenital Heart Disease: A Preliminary Report*, Oglesby Paul and Gordon S. Myers, Chicago

31. *The Ballistocardiogram: Normal Standards and Determinants of the Waves*, Richard Gubner, Manuel Rodstein and Harry E. Ungerleider, New York

32. *Blood Flow and Oxygen Consumption of the Brain in Coarctation of the Aorta*, Charles W. Crumpton, John H. Meyer, Julian Johnson, William A. Jeffers and Joseph H. Hafkenschiel, Philadelphia

33. *Pressure Curves from the Right Auricle and the Right Ventricle in Constrictive Pericarditis*, Tybjarg Hansen, P. Eskildsen and H. Gotzsche, Copenhagen, Denmark.

34. *Is the American Heart Association Prepared To Become a National Voluntary Public Health Agency?*

35. *The Clinical Syndrome Produced by Valvular Pulmonic Stenosis with Intact Ventricular Septum and Patent Foramen Ovale*, Mary Allen Engle, Helen B. Taussig and Caroline Bruins, Baltimore

36. *A Method for Visualization of the Coronary Arteries and Demonstration of the Site of Coronary Occlusion*, Johnson McGuire, James Helmsworth, Benjamin Felson and Ralph C. Scott, Cincinnati

37. *Diagnosis of Posterior Myocardial Infarction with the Aid of Semidirect Leads from the Back and Esophagus*, Charles H. Sears and Gordon B. Myers, Detroit

38. *Heart Disease Case Finding with 70 Mm. Photofluoric Films*, David D. Rutstein, Charles R. Williamson and Felix E. Moore, Jr., Boston.

PANEL DISCUSSION: Aids to Cardiac Diagnosis.